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ALBANY, N. Y.

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NOTE.

THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1907-'08. Some of these have appeared elsewhere, but for the sake of uniformity have been reprinted from the Bender Laboratory Number (January, 1909) of the ALBANY MEDICAL ANNALS. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE.

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BENDER HYGIENIC LABORATORY
INCORPORATED
1895

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Richard M. Pearce, M. D.

Richard M. Pearce, M. D.

Director 1903-1908

Dr. Richard M. Pearce was appointed director of the Bender Hygienic Laboratory, September 1, 1903. Leaving his position with the pathological department of the University of Pennsylvania, Dr. Pearce came to Albany and began at once what proved to be a most successful and satisfactory work. In the Albany Medical College he became an able and efficient teacher of pathology, bacteriology and histology and was elected to full professorship after his first year, which position he held with credit to the Medical College and honor to himself until his resignation, September 1, 1908. The contract work done by the laboratory under Dr. Pearce for the State of New York and the city of Albany in the examinations of water, blood, sputum, cultures, etc., was well and promptly done and gave entire satisfaction. In addition to the teaching, state and city work, autopsies and pathological work, Dr. Pearce carried on an independent line of research work, much of which was published and is a distinct contribution to scientific medicine. The marked business ability and executive skill of Dr. Pearce contributed much to the financial success of the laboratory during his directorship.

As evidence of their high appreciation of his sterling worth, this minute is hereby inscribed by the Trustees of the Bender Hygienic Laboratory.

Original Communications

THE APPEARANCE OF GLYCURONIC ACID IN CERTAIN CONDITIONS OF DIMINISHED OXIDATION.*

By C. W. LOUIS HACKER, M. D.

Instructor in Surgical Pathology, Albany Medical College.

Considerable scientific interest has recently been aroused with reference to the origin and importance of glycuronic acid or its conjugate salts in carbohydrate metabolism, and especially in diabetes mellitus. Paul Mayer, in a series of papers, advanced the view that since glycuronic acid represents the first step in the progressive oxidation of dextrose into CO_2 and H_2O, this compound would necessarily appear as an incompletely oxidized product of dextrose combustion when, as in the incipient stages of diabetes, the body was beginning to lose its power to oxidize the carbohydrates. In substantiation of this Mayer[1] presented the results of the study of some cases of so-called incipient diabetes and of dyspnea in which he detected the elimination of glycuronates in quantities far in excess of the normal. So far as I am aware, no further notice of this point has been taken clinically, although, theoretically considered, the presence of this compound in the urine would be an invaluable aid in indicating early stages of diabetes.

This short communication deals with the search for glycuronates in the urine of patients exhibiting glycosuria of diabetic or other origin and of those who had undergone operations in which ether or chloroform had been employed. It is well known that under conditions of anesthesia the organism finds itself in a state of diminished oxidation and also that at such times, more especially after the use of chloroform, the urine voided after operation not infrequently shows a positive (?) reaction to Fehling's test. With these points in mind, it seemed advisable to conduct a second series of tests on urine eliminated under these various conditions and to attempt to decide to what could be attributed the reducing power noticed.

---

* From the Department of Physiological Chemistry, Bender Laboratory. This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association. The earlier part of the work was done in collaboration with Dr. H. E. Robertson, formerly an assistant in the Bender Laboratory, who made a preliminary report at the Boston meeting (1906) of the American Medical Association. Published also in *Jour. Am. Med. Assoc.*, 1908, L, 252.

[1] Mayer (Paul); Unvollkommene Zucker oxydation im Organismus, *Deutsche Med. Wochschr.*, 1901, No. 16, 243; ibid., 1901, No. 17, 243; ibid. 1901, No. 17, p. 262.

Methods.—In the first series of tests the glycosuric urines were examined quantitatively as follows: By means of Fehling's and Gerrard's titration methods, by Lohnstein's newest model of saccharometer and by polarization before and after fermentation.

In the second series of determinations qualitative examination was made before and after yeast fermentation, using Fehling's, Nylander's, phenylhydrazin, orcin and polarization tests. In this way it was expected that the appearance of any substance other than dextrose could be detected. In connection with the postoperative urines a portion voided within twenty-four hours preceding the operation was examined as a control in the same manner as the postoperative sample. The anesthetics were given in the usual way, with the exception that when chloroform was employed oxygen was administered in a more or less uniform ratio to the anesthetic, this ratio depending on the character of the operation. On the average the administration amounted to fifteen minims of chloroform and three to four liters of oxygen per minute.

Before the results are discussed it becomes essential to call attention to some points as regards the manner in which the various tests were performed. No qualitative copper test for dextrose in the urine is so widely employed as Fehling's, while, at the same time, none is so carelessly performed. As a result, ambiguous findings are constantly obtained and errors in diagnosis frequently occur. The main purpose in view, when the test is applied to the urine, is to detect the presence of dextrose as against other reducing bodies, i. e., uric acid, creatinin, pentoses, lactose, etc. Since grape sugar is capable of reducing copper much more readily than any of the other compounds which might simulate it, the most suitable conditions for the test are as follows: First, the copper should exists in its most active or ionized condition; second, the quantity of the other reducing substances in the urine must become reduced to such a minimum that they are powerless to transform the copper while the amounts of dextrose still present remain active; third, the mixture should never be boiled after the addition of the urine. The first two conditions are met when the Fehling's solution is diluted and the urine added in much smaller quantities than is usually suggested in the various text-books on urinary analysis. The third is easily accomplished, although sufficient importance is not usually attached to it.

The disadvantages of using large amounts of urine (an equal or even one-half volume of the Fehling solution) are two-fold. In the first place, the strongly alkaline copper solution, especially in urines of high specific gravity, throws down a more or less voluminous precipitate of cupric phosphate which takes out the blue color of the solution and changes it to a dirty dark green. In the second place, the alkaline solution, acting on the ammonium salts of the urine, liberates sufficient ammonia to hold in solution small amounts of the red sub-oxid, obviously interfering with the detection of traces of dextrose. Reductions obtained under such circumstances are never typical. Very frequently under these conditions, and particularly if the mixture has been boiled even for only a few seconds after the addition of the urine, the greenish solution slowly takes on a dark, yellowish brown color, then becomes more turbid, and eventually, on standing, there separates out a finely divided, opalescent, yellowish green, cloud-like precipitate, which only settles out completely after the tube has been allowed to stand over night. In certain cases this reaction does not begin until a few minutes have elapsed after the addition of the urine. Such a reaction may be termed a pseudo-reaction. We recently had occasion to observe such changes occurring in concentrated urines of dogs even after the addition of only eight to ten drops of urine.[2] It is our conviction that this reaction is not due to the presence of an excessively large quantity of any weak reducing compound, such as may occur in the urine, but rather to the presence of one or more various conditions, a few of which are outlined above. The partial reduction of the copper occurs from causes other than the presence of dextrose, since, in the great majority of such cases, when the following details are observed, this obscure reaction never takes place.

The method of testing urines qualitatively for dextrose, as I employ and recommend it, as reducing to the lowest minimum the possibility of the above errors in results, and as efficient in easily detecting dextrose in amounts as low as 5/100 per cent., as well as in eliminating the reducing action of other compounds, is as follows: The sample is first tested carefully for coagulable proteids; if these are found to be present they are removed by heat and acetic acid. About four to five cubic centimeters freshly prepared, three times diluted Fehling's solution is brought just to the boiling point and immediately two drops of the proteid-free urine are added and the tube shaken thoroughly. If the urine contains over two per cent. of sugar a yellowish-red precipitate immediately appears, changing gradually to a brownish red or bright red and which settles out slowly, leaving a greenish-blue supernatant fluid. Under these conditions it is better to roughly dilute the urine with two to four volumes of water, according to the strength of the reaction, and to perform the test again.

---

[2] Pearce, R. M., and Jackson, H. C., The Production of Cytotoxic Sera by the Injection of Nucleoproteids, *Jour. of Infect. Dis.*, 1906, III, 742

With strengths of dextrose of from one-half to two per cent., two drops of urine tested as above will cause a characteristic precipitation of red sub-oxid of copper about which there can be no doubt. With the smaller percentages the change may come slowly, but even then heat need not be applied after the urine is added. The blue color of the unchanged Fehling's solution takes on a greenish hue and a turbidity appears which makes the mixture look somewhat smoky. This is caused by a very finely divided yellowish or red precipitate appearing in the blue solution. Little change may be seen by transmitted light, but by reflected light a brownish-red tint is evident, which finally develops into a decided light red precipitate, gradually settling out and leaving a clear blue supernatant fluid. Such a change is, of course, the typical Fehling's reaction, and when the test is performed with such diluted urine as above indicated the reaction can only be ascribed to dextrose. The pentoses, lactose and even maltose, by this method, do not give this characteristic reduction. Urines showing this reaction always give a reaction with Nylander's solution.

If no change occurs in the Fehling's solution after the addition of two drops, as above, the mixture may again be warmed just to the boiling point, and from two to four more drops added and the mixture observed. This should be repeated until in all twenty drops have been added. If nothing occurs at this point the urine does not contain dextrose to the extent of five-tenths per cent. As a routine, one then adds about one-half as much Fehling's as there is urine, boiling for ten seconds in order to obtain, if possible, the psuedo-reaction described above. This occurred in five per cent. of the normal urines tested by us. The time at which it appears on standing, and the depth of the turbidity and yellowish-green opalescence varies in a manner the cause or reason for which we are as yet unable to explain absolutely.

Considerable success has also been obtained in the use of Gerrard's[3] solution as a possible substitute for Fehling's quantitative procedure; while, perhaps, a little more cumbersome in its preparation than Fehling's solution, the sharpness of the end point in the titration is so greatly increased that it can be employed in some urines where Fehling's solution is impossible. Since the solution has found so little recognition in the American text-books, I detail its preparation and use.

Dilute 100 cubic centimeters of Fehling's solution with about 300 cubic centimeters of water; boil this mixture, at the same time adding cautiously an approximately five per cent. solution of potassium cyanid until the blue color has just disappeared. Then dilute the mixture to 500 cubic centimeters with water and keep in a stoppered bottle in the dark. For the titration take fifty cubic centimeters of this solution and add ten cubic centimeters of Fehling's solution. Boil the solution in a porcelain dish and run in from a burette the urine diluted so that the dextrose strength is approximately one-half to one per cent. The complete reduction of the urine is evidenced by the complete decolorization of the blue mixture. The end point is the same as in Pavy's procedure, without the disadvantageous presence of ammonia. As the double copper cyanid undergoes no reduction, the calculation takes place in the same manner as in Fehling's method, in which ten cubic centimeters are also employed. This method has been controlled with Fehling's procedure and the two give identical results. Gerrard's method is, however, the easiest to perform.

Newmann's[4] orcin test, serving to distinguish the pentoses, glycuronates and dextrose, has been extensively employed and with considerable success. Three cubic centimeters of the urine are treated with ten drops of a five per cent. alcoholic orcin solution and ten cubic centimeters of glacial acetic acid. The mixture is then brought to the boiling point and, after cooling, concentrated sulphuric acid is added, drop by drop, with shaking, until about twenty drops have been added. In the presence of pentoses the color becomes olive green, glycuronates turn the color violet and dextrose gives a carmine.

---

[3] Gerrard, (A. W.): Cyankupferreagens z. Bestimmung d. Glucose, *Jour. de Pharm. et de Chem.*, 1896, 3, 250· *Chem. Centrbl.*, 1896, 2, 135.

[4] Newmann, (A)., Neue Farbenreaktion der Zucker, *Berl. klin. Wochschr.*, 1904, No. 41, 1073.

The other tests mentioned above were performed in the usual manner.

RESULTS.

In the first series of examinations 384 samples of supposedly normal urine of patients in the hospitals of Albany were examined in the hope of finding the pseudo-reaction mentioned above and of connecting it with the presence of glycuronic acid or glycuronates. In no case could there be determined the presence of these latter compounds in amounts more than the normal or sufficient to render it of value for diagnostic purposes.

Fourteen various samples of glycosuric urines were quantitatively examined, with the following results: Gerrard's and Fehling's quantitative methods agreed to within one-tenth per cent. The results by the saccharometer were uniformly lower and usually by one-tenth to seven-tenths per cent. This difference agreed, however, with surprising accuracy with that found in the polarization determination before and after fermentation. The figures obtained by subtracting the results of polarization before and after fermentation correspond to saccharometer readings to within one-tenth per cent.

These facts indicate that both quantitative copper tests include substances which are not dextrose and which turn the plane of polarized light to the left to the extent of from one-tenth to seven-tenths per cent. (calculated as dextrose). The saccharometer readings do not include these compounds, hence they are not fermentable. As a conclusion from these examinations we may say that in these urines glycuronic acid or its salts was not present in excessive amounts.

In the second series of examinations attention was turned to the postoperative specimens in the hope that in the condition of diminished oxidation following anesthesia glycuronates might be detected in abnormal amounts. All the samples were voided within twelve hours after operation. In all 273 specimens were examined, of which 261 were voided after ether anesthesia, eleven following chloroform and one after a mixture of the two. Examination of the urines previous to the operations showed no reducing compounds to be present. Subsequent to the operations eleven samples of urine, voided after ether, gave positive reductions with Fehling's test, and on further investigation the reducing substance was shown to be dextrose in amounts from two-tenths to one and three-tenths per cent. The length and character of the operation apparently has no effect on the amount of dextrose eliminated. The patients were persons from twenty to thirty-five years of age. None of the chloroform samples or the chloroform-ether sample resulted positively. This is probably to be explained by the use of oxygen during the operation, thereby preventing diminished oxidation in the tissues.

CONCLUSIONS.

1. Dextrose appeared in four per cent. of 261 samples of urine collected after operations in which ether was employed.
2. Neither glycuronic acid nor its conjugate salts are eliminated in the urine under conditions of diminished oxidation, such as occur during diabetes mellitus and ether or chloroform anesthesia, when the latter is combined with oxygen.
3. The pseudo-reduction obtained in about five per cent. of normal urines is to be ascribed to faulty methods of performing the test. It is not due to an increase in amount of uric acid or creatinin.

A CLINICAL STUDY OF HYPERNEPHROMA, WITH PATHOLOGICAL REPORTS.*

By GEORGE E. BEILBY, M. D.

Assistant Attending Surgeon, Albany Hospital.

Since the recognition by Grawitz (1), in 1883, of the adrenal origin of a certain class of tumors arising in the kidney, there has appeared an abundance of literature bearing upon the subject. Grawitz's views were, at first, vigorously opposed by Sudeck (2), Driessen (3), Hansemann (4), Hildebrand (5), and other writers of note, who maintained that these tumors were of endothelial origin and denied the possibility of their relation to the adrenal body or aberrant adrenal tissue. Later studies, however, entirely confirmed the views of Grawitz; so that, at present, we have a well-recognized type of tumor arising from adrenal tissue, which may spring from a normally placed adrenal body, or from aberrant adrenal tissue. The term "hypernephroma," as a designation of this class of tumors, was first employed by Birch-Hirschfeld (6), in 1896, who recognized "typical and atypical, or benign and malignant hypernephromas, and, according to their origin, cortical and medullary forms." This term has come to include tumors of this character occurring not only in the kidney, but arising from adrenal rests outside of the kidney tissue; so that, at present, while it may be said that the histogenesis of these growths is thoroughly established and their pathological anatomy fairly well determined, they are among the most difficult of recognition and their clinical course and symptoms are not well defined.

The importance of early recognizing these tumors is apparent. As a rule, in the early stages they are of a benign nature, and their growth slow; and it may be months, or even years, before they metastasize, or present other signs of malignancy.

It is, therefore, mainly with the hope of adding something to the meager clinical data which we possess in regard to this condition, rather than with the idea of adding to our pathological knowledge, that this series of cases is presented.

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* Published also in *Surgery, Gynecology and Obstetrics*, 1908, (Sept.), li, 279.

CLASSIFICATION OF CASES.

Under the general term of hypernephroma are included all tumors arising from adrenal tissue, whether this be at the normal site of the adrenal gland, from adrenal "rests" within the kidney substance, or at remote localities throughout the body. Further classification upon a purely histological basis has been attempted by some pathologists. Thus, Ohlmacher (7) designates a cortical and a medullary hypernephroma, depending upon whether the new growth reproduces the cortex or the medulla of the adrenal. This author reports a case of "malignant medullary hypernephroma." I have been unable to find other cases of this character in the literature, and the cases reported in this series have the histological appearance of the cortical rather than the medullary portion of the adrenal, with one possible exception. It is probable that the medullary form of growth is extremely rare, but future observations may enable us to develop a classification upon a histologic basis.

It seems that we might properly designate, at least clinically, a benign and a malignant form, for it is well known that many of these new growths may exist for years without presenting evidences of malignancy, while others rapidly invade the surrounding tissues and metastasize early; the latter group, however, may represent but a second stage of the former.

Material. The material forming the basis of this report comprises eleven tumors removed surgically, and examined at the Bender Laboratory during the past twelve years, and four autopsy specimens, which have accumulated during a like period of time. In two of the four post-mortem cases the hypernephroma, which was small, occupied the normal site of the adrenal body. Their presence was not suspected during life, the patients having died of some other disease. In the other two autopsy cases the hypernephroma arose within the kidney, in one of which were revealed two definite types of growth—sarcoma and hypernephroma, with metastases of the former growth to the liver. An attempt has been made to obtain, as far as possible, complete clinical histories of the surgical cases and the ultimate results in each instance.

These tumors may be divided as follows:

1. Hypernephroma (or adenoma) of the adrenal body (non-

malignant), two cases; in one instance the growth was bilateral.

2. Hypernephroma of the kidney (hypernephroma renis), nine cases.

The two cases of adrenal hypernephroma (adenomata) were discovered at autopsy. In one case (Bender Laboratory Records, autopsy No. 0-848), that of a woman aged sixty, death was due to chronic diffuse nephritis and thrombosis of the superior longitudinal sinus. The right adrenal measured 4 x 4.5 x 1.5 cm., and within its medullary portion was an oval yellowish mass, measuring 1 x 2 x 2 cm., surrounded by well-defined adrenal cortex. The mass was apparently a small adrenal tumor. Its cut surface was greyish-yellow in color. Microscopical examination showed the tumor to be composed of adrenal tissue.

The other case was one of dementia paralytica (Bender Laboratory Records, autopsy No. 0-497). Male, age not stated.

Anatomical diagnosis. Arteriosclerosis of aorta, iliac, and coronary arteries. Brown atrophy of heart, with slight interstitial myocarditis (papillary muscles). Senile emphysema of lungs with healed tuberculous foci and acute bronchopneumonia. Slight chronic passive congestion of liver. Bilateral hypernephromata (adenomata) of adrenals. Here both adrenals showed the presence of new growths, the one in the left small, but in the right the growth forms a distinct nodule eight millimeters in diameter, which is composed of yellow, cortical substance.

In neither of these cases do the records show that the adrenal growth presented any symptoms during life which could be attributed to their presence. They are reported in this connection only to complete our series.

Hypernephroma renis. Nine cases. Surgical seven, autopsy two. During twelve years, in which time 1,200 autopsies have been performed at the Bender Laboratory, we have encountered but two instances of hypernephroma having its origin within the kidney. While I have been unable to obtain any clinical data of these cases, the pathological reports seem of sufficient interest to warrant recording.

CASE I. Autopsy by Dr. Blumer (Autopsy Records, autopsy No. 11). Only a partial autopsy was made about thirty-six hours after death. Aged male.

Adrenals. Normal.

Right kidney. Capsule strips off with some difficulty, tearing away small pieces of kidney substance. The surface shows well-marked fetal lobulations. It is finely granular and somewhat congested. At one point, a cyst the size of a walnut, and containing a clear fluid, projects from it. On section, the cortex is considerably diminished. Cortex markings indistinct. Glomeruli visible and pale. Medulla congested, but otherwise normal. Pelvis normal.

Left kidney. The position of the left kidney is occupied by a mass the size of two fists. It has, in general, a kidney shape. Its surface is coarsely lobulated, and is adherent to the surrounding structure by firm adhesions. Its consistence is moderately firm. On section, it presents a mottled appearance. Its main bulk is made up of a greyish-white, translucent, homogeneous structure. Here and there, are areas of this structure which have taken on a greenish color, presumably the result of degeneration. This appearance varies from greenish to a dry, chrome yellow, the tissue in the latter event resembling very strikingly the appearance of the cortical adrenal substance. The adrenal gland on the same side is attached to the tumor mass, but apparently not invaded by tumor substance. At one point is an area, some three centimeters in each direction, lined by smooth, mucous membrane. This lies in the part of the tumor which corresponds to the hilum of the kidney, and is presumably the remains of the pelvis. Considerable portion of medulla of kidney remains unchanged, growth springing from cortex.

Aorta shows extensive atheromatous changes, with marked calcification.

Liver. The organ has a peculiar shape. Right lobe is much elongated in downward direction. Left lobe is very small. Surface is free from adhesions, a brownish-red color. Scattered over the surface are a number of yellowish, slightly elevated nodules, varying in size from a pea to a marble. On section, the organ is somewhat cloudy. Nodules seen on the surface are found to extend into the substance of the organ. The depth of their extension generally corresponds to their surface diameter. Scattered through the substance of the organ in its depths are a number of similar nodules. On section, they have a homogeneous, whitish-yellow, translucent appearance. The walls of the gall-bladder are thickened. It contains small amount of thick, mucus-like material and three or four dark, facetted gall-stones the size of marbles.

Anatomical diagnosis. Primary sarcoma of left kidney. Metastases to liver and retroperitoneal glands. Chronic diffuse nephritis with cyst formation. Cholelithiasis. Hypertrophy of the prostate. Contracted bladder. Atheroma of aorta.

THE TUMOR.

The tumor presents, in different parts of its substance, two entirely different structures. In places one type predominates over a large area; in places the other type predominates over a large area; while, in still other places, the two adjoin each other, the one apparently invading the other, as will be described below. The one type of tumor presents the following appearances: Under the low power, it is apparently made up of a series of fairly regular spaces, having thin walls, and containing a few scattered nuclei. Under the high power, it is seen that the walls of these spaces are made up of fine bands of connective tissue. The spaces are lined, in some places, by flat cells similar to those lining those of normal blood or lymph vessels. The scattered nuclei, which were seen with the lower power in the spaces, can now be made out to belong to large, exceedingly pale cells, which fill the spaces, and which are apparently proliferated endothelial cells. At no place in the section, which is an alcohol-hardened one, can red blood corpuscles be seen, notwithstanding the fact that their shadows can easily be made out in the adjacent vessels. At one or two places in the tumor spaces are objects which suggest shadows, and, in an occasional space, the polynuclear leucocytes may be seen. There are distinct blood-vessels running through the tumor, but no connection can be made out between them and the spaces. Although the tumor presents all the appearances of an angiosarcoma, it seems probable that it sprung from the lymph and not the blood vessels.

The other type of tumor, present in the growth, is made up of cells without any definite arrangement, between which run irregular bands of connective tissue. The cells in this growth vary considerably in size and appearance. Taken as a whole, they are large cells. Their shape varies, some being round, some oval, and many of them quite irregular. The amount of protoplasm varies, some showing but a narrow rim, while in others the amount is great. The nuclei have a peculiar refractive look, and the chromatic network is very sharply marked. Scattered throughout the tumor are quite a number of multi-nucleated cells, many of which are large enough to deserve the name giant cell, and some of which have distinct budding nuclei, such as are seen in certain cells of the bone marrow. Where the two types of tumors meet, one gets the impression that the angiosarcoma is being invaded by the other growth, and the invasion is apparently taking place by the progression of the latter along the connective tissue of the former.

Liver. Outside of the metastasis to be described later, the liver shows areas of localized dilatation of the blood-vessels (probably from pressure of tumor nodules), a swollen and granular condition of the liver cells, and occasional fat spaces. The tumor metastasis, which causes a certain amount of compression of the surrounding liver substance, resembles the second type of growth described. The cells, however, do not differ nearly so much in size as they did in the original growth, nor are there present any such number of the large multinuclear cells, or of the cells with budding nuclei. In fact, both of these latter are almost absent.

Kidney, for some reason, stains very poorly. Capsule absent. Occasional areas or new-formed connective tissue in center and few similar areas in kidney substance. Most of the glomeruli normal. Here and there, an atrophied one is seen. Kidney cells swollen and granular. Blood-vessels show well-marked obliterative endarteritis. Occasional hyaline cast is seen in tubules.

Case 2. Autopsy by Dr. Pearce (Autopsy Records, No. 1147). Male, sixty years of age.

Abdomen. A small amount, about 300 cubic centimeters, of clear, straw-colored fluid is found in the pelvis. Appendix normal. Mesenteric lymph-nodes normal. In the left flank is found a large, lobulated mass, corresponding to the position of the kidney, and adherent to the adjacent structures.

Right kidney. Smaller than normal. Capsule peels readily, leaving a coarsely granular surface, with here and there a few small cysts. Cortex is greatly diminished, being less than one-half the normal amount, and is firm and greyish-red in color. Pyramids are injected. In the pelvis is an increased amount of fat. On the surface of the kidney, and projecting from it as a globular mass, is a tumor two centimeters in diameter, of soft consistence, uniformly yellowish in appearance, and distinctly encapsulated.

Left kidney is similar in appearance to right, but adherent to and involving its upper pole, is a bilobed mass, twice the size of the kidney itself, which is soft and fluctuant and suggests the presence of cysts. On section, however, these masses are found to consist of a new growth, which has become completely necrotic and which presents in part a uniform, rather firm, yellowish, necrotic tissue, and, in part, soft, red, grumous material mixed with old blood. The position of the tumor, which is distinctly encapsulated and separated from the kidney substance, although it impinges upon the kidney, presents here and there small portions of tissue which have not undergone necrosis and which indicate it to be of adrenal origin. Moreover, the adrenal on this side cannot be found.

Anatomical diagnosis. Arteriosclerosis. Chronic diffuse nephritis (interstitial type). Fatty transformation of the myocardium. Large necrotic hypernephroma involving left kidney. Small hypernephroma of right kidney. Subacute esophagitis. Chronic congestion of liver. Emphysema of lungs. Moderate hydroperitoneum and hydrothorax. Malformation of sternum (old fracture?).

Microscopic diagnosis. Chronic interstitial nephritis with hyaline degeneration. Subacute esophagitis. Papillary adenoma of kidney. Necrotic hypernephroma.

Surgical Cases.

Case 1. Male, aged fifty-eight, was admitted to my service in the Albany Hospital, October 10, 1907. His family history was unimportant. He states that he has always been in good health till the onset of the present trouble, which began seven years ago. At this time, while picking fruit in a tree in a strained position, he felt something "give way" in his right side. The sensation was so noticeable that it was mentioned to his wife.

Two days later, blood appeared in the urine, and persisted for two or three days, but was not accompanied by pain. The patient experienced no trouble for a year and a half, during which time he felt perfectly well, when there appeared a second attack of hematuria of greater severity than the first and its onset was accompanied with colicky pain and chills, the pain radiating from the back to the perineal region and penis. The flow of blood was so profuse that clots obstructed the urethra and catheterization was necessary. This attack continued for about a week, when there was complete cessation. From this time until about six months ago (four and one-half years), the attacks of hematuria recurred at intervals of four or six months, each time lasting from two days to a week. During the last six months they have occurred more frequently. From frequent catheterizations the patient has developed a severe cystitis. During the last year he has lost about ten pounds in weight.

Physical examination. The patient is a strong, muscular man, well nourished, with a slightly sallow complexion. The superficial arteries show no signs of sclerosis. Pulse eighty, strong and regular. Examination of the heart and lungs gives no evidence of disease of these organs. There is a decided fullness in the right flank below the costal margin where, on palpitation, a tumor, measuring approximately ten by eighteen centimeters, can be made out. It occupies the lumbar region and extends forward to the nipple line. It moves slightly with respiration. It presents a smooth, anterior surface, and suggests in its shape and position a tumor involving the kidney. A skiagraph was made and at about the center of the tumor mass a small shadow, about the size of a pea, was seen, which was interpreted as revealing a small kidney stone. In view of the history and X-ray findings, a clinical diagnosis of cystic kidney was made.

Urine examination. Sp. gr. 1018, acid, no sugar, trace of albumen, pus and epithelium abundant.

Operation, October 12. Chloroform and oxygen. Lumbar incision. Kidney was found adherent to the surrounding fat, from which it was separated with considerable difficulty. On account of its size, the mass could not be delivered until the incision was extended well forward along the ilium. The pedicle of the kidney was clamped and the organ removed. On account of the extensive involvement of the vessels by the new growth, their ligation was impossible. Clamps were left in situ. Several large gauze wicks were carried down to the stump of the renal pedicle, and the external wound partially closed with interrupted silkworm gut sutures. Salt solution 1,000 cubic centimeters were given subcutaneously. There was considerable operative shock, but the patient responded well to treatment, and his condition after twelve hours was good. During the first twenty-four hours following the operation, only three and one-half ounces of urine were obtained per catheter. By the employment of diuretics and the introduction of large amounts of saline solution, the daily output of urine was gradually increased, so that on the sixth day after the operation thirty-eight ounces were obtained, which had a fair specific gravity, but contained a large amount of albumen. The patient early developed symptoms of uremia and died on the seventh day after operation.

Pathological report (Bender Laboratory Records, Surg. Path., No. 07-1348. See Fig. 1).

Gross description. Specimen consists of a kidney, measuring 14 x 8.5 x 7.5 centimeters. Outer surface is very irregular, in places of a nodular character. It is throughout the greater part mottled greyish-red in color, nodules being bright yellow. At hilum these nodules are more marked, and a mass measuring four centimeters in diameter, apparently having its origin in the pelvis, is present beneath the capsule. These nodules vary in size, from pin point to the above mentioned. Some are solitary, while others are conglomerate. On section, the pelvis is considerably dilated and distorted and, in part, the calices are obliterated. Cut surface of the kidney substance shows it to be pale greyish-brown in color, and anatomical markings are obliterated. Distributed throughout are numerous, slightly elevated, yellow areas of various shapes and sizes. These nodules are somewhat firm, but one has broken down and presents slight hemorrhage. About some of these nodules the tissue is dark brown, due to old hemorrhage.

Anatomical diagnosis. Multiple hypernephromata of kidney.

Microscopic description. Sections of kidney. The entire cortex and medullary portions are extensively replaced by connective tissue, the greater portion being composed of young cells. Many tubules are compressed and obliterated, some containing hyaline casts and denuded of epithelium. Others are dilated. Many glomeruli are partly or entirely replaced by fibrous connective tissue and the capsules greatly thickened. In the section are areas of cuboidal cells which stain poorly and contain fat globules. These nuclei are found and show no definite arrangement. About them the connective tissue is fibrous and contains considerable free blood and pigment.

Microscopic diagnosis. Hypernephromata of kidney.

Autopsy by Dr. Hacker (Bender Laboratory Records, autopsy No. 1188).

Anatomical diagnosis. Absence of right kidney (due to operation). Incised wound of right side, with necrosis (due to operation). Hypernephroma of perinephritic fat (right side), with invasion of inferior vena cava. Chronic interstitial nephritis. Cholelithiasis. Hydroperitoneum. Hydrothorax. Hypostatic congestion of left lung. Emphysema of lung. Anthracosis of lung.

Kidneys. The left kidney is enlarged and measures 11 x 6.3 x 5 centimeters. The capsule, in places, is adherent. The surface is pale and presents numerous points of retraction. Beneath it are occasional cysts, the largest one centimeter in diameter. The cut surface is pale and opaque. The cortex is thickened and markings are indistinct. Numerous cysts are present, and at the lower pole in one pyramid is a circumscribed, soft, brownish-yellow nodule one and two-tenths centimeter. The right kidney is absent. In the right renal region the tissue is infiltrated by blood and necrotic material. Behind the right renal vein is a soft, friable mass, measuring approximately 5 x 3 x 2 centimeters. The portion bordering on the wound is soft, pinkish-brown, but anteriorly it is soft and bright yellow. The latter penetrates the posterior wall

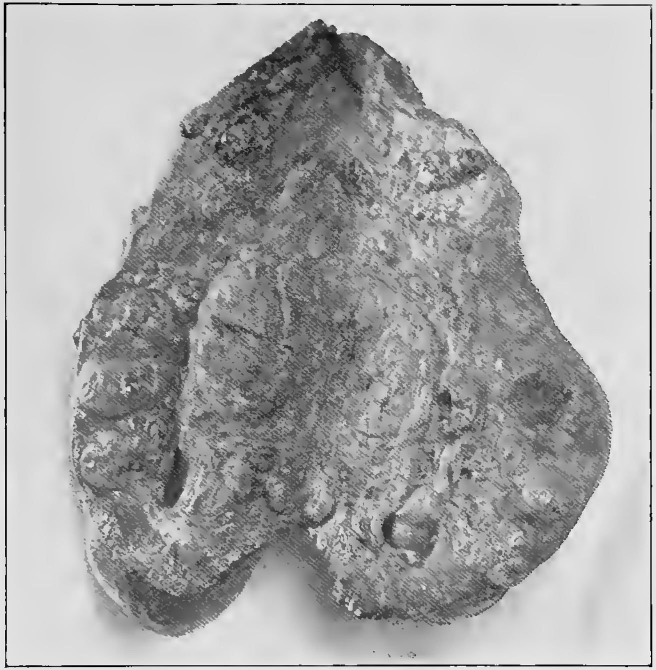

FIG. I. Photograph of Multiple Hypernephromata of **Kidney.** $\frac{3}{4}$ actual size. Surgical Case I.

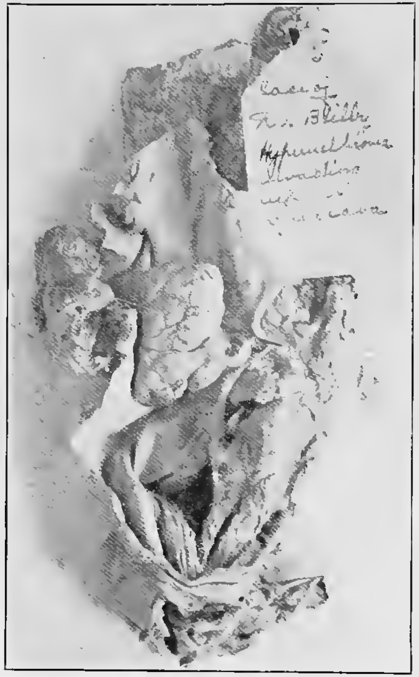

FIG. II. Photograph Showing Hypernephroma Invading Vena Cava. $\frac{3}{4}$ actual size. Case I.

of the inferior vena cava and forms a pedunculated mass, which fills the lumen and extends into both renal veins (See Fig. 2). This mass is soft, bright yellow, and freely movable about the pedicle. It measures approximately 4 x 3 x 1.8 centimeters. About four centimeters from the inferior vena cava, the right renal vein presents a small, bluish-brown, eroded area.

Microscopic description. Right kidney. Throughout there is an irregular increase of connective tissue and beneath the capsule are areas composed chiefly of small, round cells. In the cortex, many of the tubules are lined by swollen and granular cells, which entirely fill their lumina. Toward the pelvis, many are contracted and filled with hyaline material. Others are dilated. The lumina of many tubules are filled with desquamated epithelium. Many cells contain fat globules. Many glomeruli show proliferation of young connective tissue, some of which are entirely transformed into fibrous tissue with hyaline degeneration. The veins are engorged and dilated. The arteries show thickening, chiefly the intima, while many capillaries show obliteration with hyaline transformation. At one point is an area composed of processes of fibrous tissue covered by cuboidal cells, many of which have a brown granular material. In places these processes have undergone necrosis. Within the necrotic material are numerous blood corpuscles, pigment, and cholesterin spaces. About this area is a dense, fibrous capsule in which are a few spaces lined by a single layer of cuboidal cells. The nuclei of these cells are round and stain deeply. In the region of this area are several cysts containing a mucoid substance. These cysts are lined by a single layer of low cuboidal cells. Throughout many sections are occasional small areas filled with densely packed, irregularly arranged cells, which resemble in structure those in the area above described. The arteries show marked thickening of the intima and the capillaries show increase of connective tissue, with hyaline transformation and obliteration.

Left adrenal. Irregular areas are composed of cells showing marked infiltration of glycogen. The capillaries show marked thickening with hyaline transformation. Many are obliterated.

Right adrenal. Similar to left.

Retroperitoneal mass at base of wound. The greater part is composed of large cells having a tubular arrangement and in which are globules of glycogen. The greater part of the tissue is necrotic and the capillaries are distended with colonies of bacteria. In part, the necrotic material is markedly infiltrated by polynuclear leucocytes. The remaining tissue is edematous and contains many leucocytes.

Microscopic diagnosis. Hypernephroma of lumbar region, with necrosis and suppuration. Hypernephromata of right kidney. Chronic interstitial nephritis. Chronic myocarditis. Chronic passive congestion of lung, liver, and spleen. Arteriosclerosis. Chronic cystitis. Slight chronic pancreatitis. Acute bronchopneumonia. Anthracosis, emphysema, and atelectasis of lung. Encapsulated papillary adenoma of right kidney.

Case 2. Service of Dr. MacDonald. Mr. T. S., aged forty-six years. Duration of disease six months, following a fall in which he was struck in the region of the right kidney. Symptoms of onset, pain, originating in right lumbar region and referred downward to penis, hematuria accompanying pain. Recurrent attacks for six months.

Clinical diagnosis. Stone in kidney.

Operation. Removal of right kidney.

In February, 1908 (five and one-half years after operation), patient was in good health.

Pathological report (Bender Laboratory Records, Surg. Path. No. 97-14), September 4, 1902.

Gross description. Specimen consists of a kidney measuring 5 x 2 x 1.5 inches. The fatty and fibrous capsules have both been removed, leaving a smooth, mottled surface. The prevailing color of the surface is yellowish-brown, the mottling being due to numerous pin-head areas of hemorrhage. The upper pole of the kidney is enlarged, and there are present on the surface of the enlarged portion a number of yellowish tumor nodules, covering from one-sixteenth to three-eighths of an inch in diameter. These nodules are rounded, soft in consistence, and smooth, and are of yellowish color. On section of the kidney, the main portion of the organ is relatively normal. The cortex is slightly swollen and quite pale. Glomeruli congested. The pelvis shows a number of discrete and confluent hemorrhages. The tumor nodule measures an inch and five-eighths in diameter. It is roughly globular and occupies one pole of the kidney and projects into the pelvis. One point of the tumor is soft, and in places distinctly hemorrhagic, and is made up of a yellowish cellular growth, which has the appearance of adrenal tissue.

Anatomical diagnosis. Hypernephroma of the kidney.

CASE 3. Service of Dr. Vander Veer. Mr. G. W., aged thirty-five. Complains of tumor in the left abdominal region. Onset five years ago, with pain in the region of the tumor. Attack lasted three days. Ten days ago, first noticed a bunch in left side of abdomen, which has increased some in size since then. Patient has lost in weight and feels perfectly well. Urinary examination showed granular, hyaline, and epithelial casts, some mucus, some epithelia, clear amber, sp. gr. 1020, no sugar, trace of albumen.

Clinical diagnosis. Sarcoma of kidney.

Operation, May, 1905. Removal of left kidney. In November, 1907 (two and one-half years since operation), patient was well. Had gained fifteen pounds in weight. Urine was normal. No evidence of metastatic or recurrent growths.

Pathological report (Bender Laboratory Records, Surg. Path., No. 05-537).

Gross description. Specimen consists of a kidney, from the cortex of which projects a definitely encapsulated cystic tumor, measuring from twelve to sixteen centimeters in diameter, and having a base measuring 10 x 3 centimeters. The center of this base corresponds to a point situated on the surface of the kidney, opposite the hilus and at a point corresponding to the junction of the upper and middle thirds. On section, the tumor is found to have a firm, fibrous capsule, averaging from three to five millimeters in thickness, and a softened center, consisting of a grumous, blood-stained, necrotic-looking material, with coarse tags of fibrous tissue extending in from the wall of the cyst. The cyst extends into the kidney as far as the pelvis and the kidney cortex is reflected over the surface of the tumor, for a distance of four to five centimeters, at the base. The remainder of the kidney shows nothing noteworthy. The general picture is that of a tumor, originally composed of large, cellular areas and coarse interstitial fibrous bands, which has undergone extensive necrosis.

Anatomical diagnosis. Hypernephroma with extensive necrosis and softening.

Microscopic description. Sections show capsule composed of dense fibrous tissue with areas of calcification and true bone formation. The contents of the cyst are, for the most part, almost completely necrotic, but immediately adjacent to the capsule, and partly infiltrating it, can be be seen irregular islands of large, polyhedral, vacuolated cells having the general characteristics of adrenal cells. These cells are arranged in irregular masses, and, in some areas, have an indefinite, glandular arrangement. In other sections, new-formed blood-vessels can be seen extending from the capsule into the necrotic, hemorrhagic cysts contents.

Microscopic diagnosis. Adrenal tumor with extensive central necrosis and softening and hemorrhage, together with calcification and bone formation in capsule.

Case 4. Service of Dr. Madill, of Ogdensburgh, N. Y. Mrs. K., aged thirty-three. Duration of disease about five months. Symptoms anemia, loss in weight, and pain of a dragging character in the region of the left kidney. No urinary symptoms (patient had suffered from neurasthenia for over a year, and the tumor of the kidney was discovered while making an examination).

Clinical diagnosis. Tumor of kidney.

Operation. Nephrectomy, left.

Recovered from operation rapidly and improved for about four months. Then again became anemic, lost weight, and died ten months after operation (definite cause of death not known. No evidence of recurrence or metastases).

Pathological report (Bender Laboratory Records, Surg. Path. No. 06-55).

Gross description. Specimen consists of a large, distorted kidney. Capsule strips fairly readily from one pole, which measures 7 x 6 x 3 centimeters. Opposite pole is enlarged by a circular tumor mass so that it measures 10 x 7 x 5 centimeters. Entire kidney is about thirteen centimeters in length. Mass is six centimeters in diameter. Kidney substance is normal in consistence, except over mass, where softened areas are felt. Considerable amount of fat is found in pelvis. Over tumor, color is a reddish to a yellowish-white. Remainder of kidney is pale and dark reddish-white in color. Cut surface shows the tumor mass to be well encapsulated, yellowish-white in color. Several areas of hemorrhage near periphery. The remainder of tumor surface contains scattered areas of increased consistence and waxy appearance. In the remainder of the kidney, cortex and pyramids are very pale. Pelvis contains a large amount of fat. Malpighian corpuscles are seen.

Anatomical diagnosis. Adrenal adenoma arising in kidney.

Microscopic description. Section of kidney and tumor mass shows tumor surrounded by a compact layer of kidney pulp, beneath which and in body of tumor are found areas of hemorrhage. Tumor is made up of a fine, reticular stroma, in which are large epithelioid cells with vesicular nuclei. Cells are arranged in cords and masses. Protoplasm does not stain well, is translucent and vacuolated, and contains a few granules. Many large areas of necrosis occur, accompanied by infiltration of leucocytes and lymphoid cells. Renal tissue proper shows cloudy swelling of tubular epithelium.

Microscopic diagnosis. Adrenal adenoma.

CASE 5. Service of Dr. Van Loon. Mrs. D. Z., aged fifty-two. Family history negative. Patient has had attacks of "stomach trouble" for several years. One week ago, a definite attack of biliary colic. Upon examining the abdomen at this time, a tumor of the right kidney was found. Urinary examination negative.

Clinical diagnosis. Gall-stones, tumor of right kidney.

Operation, May 11, 1907. Cholecystotomy, removal of gall-stones, nephrectomy, right kidney and tumor. Good recovery. In February, 1908 (eight months after operation), patient was well.

Pathological report (Bender Laboratory Records, Surg. Path. No. 07-670).

Gross description. Specimen consists of a pyramidal-shaped mass, measuring approximately 18 x 12 x 8 centimeters through its broadest diameters. The mass is encapsulated and the broader half is greyish-yellow and soft, while the remaining portion is firmer and greyish-brown. On section, the cut surface of the soft portion is pale, brownish-yellow, and pulpy; from it there exudes a brownish-pink fluid. The remaining portion, on section, presents the cut surface of a kidney. The two portions gradually fade into each other.

Anatomical diagnosis. Hypernephroma of kidney.

Microscopic description. Sections show trabeculæ and gland-like spaces, composed of polygonal or cuboidal cells, arranged in an irregular manner. In parts necrosis is seen and extensive hemorrhage.

Microscopic diagnosis. Hypernephroma of kidney.

CASE 6. Service of Dr. Macdonald. Mr. D. J., aged forty-nine. Clinical history not obtained. Patient died twenty-four hours after operation.

Pathological report (Bender Laboratory Records, Surg. Path. No. 04-860).

Clinicol diagnosis. Sarcoma of left kidney.

Gross description. Specimen consists of a much enlarged and degenerated kidney which has been bisected. Each half measures about 16 x 12 x 3 centimeters. External surface of one-half is smooth and glistening. The other surface is uneven and denuded of covering in places. On section, find but little evidence of normal kidney tissue, and that is near periphery. Surface, as a whole, presents a necrotic, honey-combed appearance. Strands of white, fibrous tissue, fairly hard to feel, radiate in all directions. These areas are intermingled with yellowish patches, some of them being necrotic and filled with cheesy-like material. In still other places, the surface presents a pearly-white appearance. Some evidence of hemorrhagic areas in cortex, there being a few blood clots.

Anatomical diagnosis. Hypernephroma of kidney.

Microscopic description. Large masses of cells with round, lightly staining nucleus and large amount of protoplasm, which is greatly vacuolated and resembles the structure of adrenal cells. Between these masses are large bands of more or less hyaline connective tissue. Some portions of tumor are entirely necrotic.

Microscopic diagnosis. Hypernephroma.

CASE 7. (From Ellis Hospital, Schenectady, N. Y.) I have been unable to obtain any clinical history of this case other than that which was appended to the specimen upon its receipt at the laboratory. It was said to be a left kidney which had been growing for seven years; patient suffered from intermittent hematuria.

Pathological report (Bender Laboratory Records, Surg. Path. No. 04-1054).

Gross description. Specimen consists of an oval tumor mass, measuring 24 x 17 x 14 centimeters. The surface is roughly lobulated and covered with coarse tags of fibrous tissue, the entire mass having a firm, fibrous capsule. On section, the mass is seen to consist of multiple globular, usually definitely encapsulated, tumor masses, ranging from one to four centimeters in diameter. These masses, are separated from one another by firm sheets of fibrous tissue which retract on section. The non-degenerated portions of the new growth present a light pink, distinctly granular, cut surface; others are softened and present a yellowish, fatty-like surface; while others are hemorrhagic, and a few are represented by cavities filled with a hemorrhagic fluid.

Anatomical diagnosis. Hypernephroma.

Microscopic description. Sections show stroma of connective tissue imbedded in which are large polyhedral cells, lying in irregular columns. These cells show marked vacuolation, with some pigmentation resembling adrenal cells.

Microscopic diagnosis. Adenoma of kidney with cells resembling adrenal cells (hypernephroma).

SYMPTOMATOLOGY.

The four cases reported from our autopsy records did not present, as far as can be determined, any symptoms attributable to the hypernephroma. The clinical history of one of the surgical cases was not obtainable, leaving us only six cases on which to base our clinical data. The symptoms of importance, which were fairly constant, were three in number, *pain, hematuria* and *tumor.* Pain was present in four of the six cases, in three of which it was of the type described as renal colic, and was accompanied by hematuria. Without doubt, the pain in these cases is due to the passage of blood clots from the pelvis of the kidney to the bladder. In the fourth case, the pain was confined principally to the region of the tumor, and radiated backward to the spinal column.

The most frequent form of pain, then, is that accompanying the hematuria, and it differs in no way from that caused by the passage of other foreign bodies along the ureters. It is usually not as severe in character as that produced by calculi. The hematuria, if slight in amount, may occur without pain. It is frequently the first symptom noticed. In all of our observations it was intermittent in character, lasting from a few hours to several days, and appearing at intervals from a few months to several years. In one case, the hemorrhage was usually very profuse, often filling the bladder with clotted blood and obstructing the urethra.

Apparently the size and location of the growth within the kidney substance had little bearing upon the occurrence of this symptom; for, in two instances where the pathological examination showed the tumor to be of large size and to involve the renal pelvis, there had been no hematuria. A tumor that is easily palpable, or that the patient discovers, is necessarily a late symptom and, if one on which we rely to make a diagnosis, often appears too late to offer our patient a good chance of recovery.

Location. In six of the ten cases of hypernephroma of the kidney, the tumor was found upon the left side.

General symptoms are usually absent in the early stages. With prolonged and severe bleeding, secondary anemia is marked, and the patient may lose considerable weight. In one case the condition was associated with neurasthenia.

Aside from the presence of blood, there were no significant urinary changes. One case had a severe cystitis, probably from catheterization, and in two there were evidences of a chronic nephritis, albumen, and urinary casts.

Age. The youngest patient was thirty-three, the oldest sixty years; average age forty-eight years. The average age of onset, as indicated by the appearance of symptoms, was forty-one years.

Sex. In one case, the sex was not stated. In six cases, it was found four times in the male and twice in the female.

Duration. It is obviously difficult to ascertain, even approximately, the length of time that many of these tumors have been present. In two of our cases, while the growths had attained large size, they had presented no symptoms which attracted the attention of the patient, and they were discovered by the physician upon examination. It is only in those cases, in which hematuria and pain are manifest, that we can base any accurate knowledge of the length of time which the tumor has been present. I think it may be said that, almost without exception, this type of growth is slow in progress, especially in its early stages, and attains palpable size only after several years of existence. In two cases in this group hematuria had been present for seven years. Tumors presenting symptoms for shorter periods of time, gave no indications, histologically, of being of a less malignant type.

Diagnosis. Unfortunately these tumors of adrenal origin, whether arising within the kidney substance or at the normal site of the adrenal body, present no pathognomonic symptoms. For a diagnosis we are largely dependent upon three symptoms, *hematuria, pain* and *tumor,* which are alike suggestive of other and more common kidney lesions. As far as I am aware, those growths arising outside of the kidney never present symptoms, except tumors and, perhaps, metastases, both of which are necessarily late manifestations. It may be said that rarely is a correct diagnosis of hypernephroma made previous to operation. This is unfortunate, since it is clearly demonstrated that these growths, at least the majority, are of a benign character in their early stages, and that, when thoroughly removed at this time, they show no tendency to recur. It seems that, clinically, we may recognize two groups of *hypernephroma renis:* Cases associated with hematuria; and cases without. Obviously, the cases without hematuria present no early symptoms whatever suggestive of renal lesion, so that in this group, *tumor* and, rarely, pain are the first manifestations. This was true in three of our six cases in all of which the growth had attained considerable size. In one of these cases, death occurred within a few days after operation, and in another, after a few months. In this latter case, while it was not demonstrated that death was due to metastases, this seemed to the surgeon to be the probable explanation. In the other group of cases where hematuria is present we are given a clue to the condition, and by a process of exclusion we should be able, at least, to make a tentative diagnosis of hypernephroma. An exploratory operation should then be done. Three of our cases had hematuria early in the disease and in each instance it was associated with "colicky" pain. In a study of the cases collected by other observers, we are led to believe that *hematuria* and *pain* are present more frequently than indicated by our series. Thus Keen and Pfahler (8) found hematuria in nineteen out of twenty-six cases. Cases, then, presenting the symptom of hematuria should always be approached with this possibility in mind, and we should exhaust every means at our command to confirm or exclude hypernephroma. A question in regard to these cases, which has never been thoroughly investigated, is that of increased arterial tension. It is logical to suppose that, with an increase of adrenal tissue, we may have an excess of adrenal secretion, which would result in a rise of blood-pressure. Certain writers have noted that this was true; but observations upon this point, sufficient to settle the question, have not yet been made. Every case of hypernephroma should be thoroughly investigated in this regard, and we may find that a study of the blood-pressure furnishes us a valuable aid in diagnosis.

Prognosis. I think it can be safely said that, in the majority of cases of hypernephroma, an early removal of the tumor will result in a complete cure. Three of our six cases operated upon are still living and in good health; in one instance five and one-half years have elapsed since operation. One case has been lost sight of.

Metastases of the hypernephromata are not uncommon, although it was not observed in any of the cases of our series. In Case 1, there was a direct extension of the growth through the renal vein into the vena cava. The usual mode of metastasis is through the blood-stream by way of the renal vein, and this takes place usually in the later stages where there is extensive local invasion. The metastases, therefore, are found most frequently in the bones, lungs, and liver. Scudder (9) has recently recorded four instances of bone metastases and refers to eleven other cases in the literature, making fifteen in all, the majority of which were fatal. Rarely, extension may occur through the lymphatics. Stober (10) reports a case of hypernephroma of the left adrenal with metastases to the mediastinal lymph glands. I have been unable to find other similar instances in the literature.

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THE INFLUENCE OF THE REDUCTION OF KIDNEY SUBSTANCE UPON NITROGENOUS METABOLISM.[1]

By RICHARD M. PEARCE, M. D.

This communication presents the results of one of several investigations having for their object the determination of the part played by chemical correlation, in a broad sense, in the productions of pathological conditions associated with diseases of the kidney.[2] In taking up such problems one of the first questions for consideration is that of the influence of the hypothetical internal secretion of the kidney upon general nitrogenous metabolism. I use the term hypothetical advisedly, for although this theory occupies a prominent place in the literature dealing with the question of uremia and is very suggestive, there is little experimental or other evidence to support it.

It was first brought to general notice by Brown-Sequard,[3] who as the result of his investigation of the internal secretion of the testicle came to very broad conclusions concerning internal secretions in general and stated that the kidney, as also other organs, have this function. He based his opinion as regards the kidney on clinical observation[4] and the study of dogs from which both kidneys had been removed as compared with those in which the ureters had been ligated. As the result of both procedures the retention of metabolites is the same, but in the nephrectomized animals, death, which comes on more rapidly, is supposed to be due to the absence of an internal secretion which, it is assumed, is still furnished by the ligated kidneys. If, as he claimed, in the nephrectomized animals the internal secretion is replaced by the injection of renal juice, or glycerine extracts of kidney or by normal serum the animals live as long or even longer than those which have had both ureters ligated. Such observations are urged in support of the theory of internal secretion by those who do not believe uremia to be due to the retention of the products of metabolism.

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[1] Aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Journal of Exper. Med.*, 1908, x, 632.

[2] Pearce, R. M., The Theory of Chemical Correlation as Applied to the Pathology of the Kidney, Annual Address before the Philadelphia Pathological Society, April 23, 1908.

[3] Brown-Sequard, Importance de la secretion interne des reins, *Arch. d. phys. norm. et path.*, 1893, v, 778.

[4] Fowler, E. P.. Suppression of Urine, New York, 1881.

Similarly, metabolism experiments on man which tend to show that uremia may occur without evident nitrogen retention are viewed in the same way and are taken by those who support the theory of internal secretion to indicate that uremia is not due to lack of elimination of metabolites but to loss of the internal secretion.

From the experimental side the only method of attack has been by the study of the variation in elimination of nitrogenous substances after extirpation of amounts of kidney substance sufficient presumably to disturb the hypothetical internal secretion. Upon this phase of the subject the observations of Tuffier, of Bradford and of Bainbridge and Beddard are available. Tuffier[5] removed first one kidney, and after an interval, a portion of the other. He came to the conclusion, based on ten experiments, that one and five-tenths gram of kidney substance per kilo of body weight was sufficient to maintain life and adds that except for oscillations due to the immediate effects of the operation no changes in the elimination of urine or urea were noted.

Bradford[6] also working with dogs, found that after the removal of approximately three-fourths of the total kidney weight death occurred in from one to six weeks from asthenia with great wasting; coma and convulsions were not observed. Death is apparently dependent on the amount of kidney substance removed and not upon mutilation inflicted by the surgi-

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Tuffier, T., Étudés expérimentelles sur la chirurgie des reins, Paris, 1889 (quoted from Bradford).

[6] Bradford, J. R., The Results following Partial Nephrectomy and the Influence of the Kidney upon Metabolism, *Jour. of Physiol.*, 1899, xxiii, 415.

cal operation. Excision of a portion of one kidney or portions of both is followed by an increase in the volume of the urine, but unaccompanied by an increase in the total solids. After excision of three-fourths of the total kidney weight there occurs an increase in the amount of urea eliminated. This increase is absolute when appetite does not fail, and relative when little or no food is taken. Under the latter circumstances the amount of urea eliminated is as great as that excreted previously on a full diet. At the same time the blood and tissues, particularly the muscles, show a considerable increase in nitrogenous extractives. Bradford concludes that the disturbance of metabolism following the reduction of kidney substance is due, not to the retention of the products of normal destruction of tissue, but to an increased tissue catabolism especially of the muscles, producing large quantities of urea. He states that he has made no observations to determine whether this is due to the cessation of the action of a renal internal secretion. His results have, however, been so interpreted by later writers.

Bainbridge and Beddard[7] in a recent publication describe their observations on cats. They conclude that the removal of three-fourths of the kidney substance causes loss of appetite, wasting and death in a few days or weeks; that an increase of nitrogen in the urine is not constant and occurs only during the last few days of life when the animal has lost twenty-two per cent. or more of its body weight and therefore that the kidney has no direct influence on metabolism but that the increase of nitrogen is the result of inanition and similar to that which occurs in starving animals. They also found that there was not necessarily an increase in the volume of urine.

The difference of opinion between these investigators seemed sufficient to warrant a repetition of the experiments in order to determine the effect of the reduction of the kidney on nitrogenous metabolism. In carrying them out I have also investigated the total nitrogen eliminated in the feces in order to determine if possible whether or not the inanition could be explained by digestive disturbances due to faulty absorption or possibly to the effect of irritating nitrogenous substances eliminated through the intestines.

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[7] Bainbridge, F. A., and Beddard, A. P., The Relation of the Kidneys to Metabolism, *Proc. Royal Soc.*, 1907, lxxix (B), 75.

These experiments were made upon dogs which were kept for some time before operation and during the entire course of the experiment in nitrogenous equilibrium. For this purpose a purin-free diet of casein, cracker dust and lard was used and the *per diem* amount of water limited to 600 cubic centimeters. The animals were kept in the usual well-ventilated metabolism cages and were catheterized at the end of each twenty-four hours. After each catheterization the bladder was washed out and the wash water added to the catheterized urine and that voided naturally and the whole made up to a definite volume. This urine was carefully preserved from changes of any kind until the analyses were made. When albuminuria caused the appearance of coagulable protein in the urine, which occasionally happened during a short period immediately following operation, this was removed by heat and acetic acid, the coagula being thoroughly boiled out with water and the washings added to the urine.

Upon these twenty-four samples the following determinations were made: Total nitrogen by the Kjeldahl method; ammonia by the Shaffer method and urea by the Mörner-Sjoquist method. The investigation was so delimited mainly because the changes in total nitrogen and in the elimination of urea and ammonia are the only points in dispute and in part on account of the negative nature of the results obtained by Bradford and by Bainbridge and Beddard in regard to other substances.

The general procedure was to place the animal in nitrogenous equilibrium, conduct control determinations for a period of three days, operate, and after allowing two or three days for recovery from the acute effects of the operation make determinations during one or more three day periods.

The operative procedure differed somewhat from that of the English investigators. Instead of removing a wedge of kidney substance the upper half of a kidney was removed and the bleeding from the cut surface controlled by a mattress suture. This method, although it narrows the pelvis somewhat, is not followed by infarction or hemorrhage and gives better results than that recommended by Bradford. At a subsequent operation either one-half the opposite kidney, or the entire kidney

TABLE I.

(*Dog 4, ¼ and ½ reduction.*)

Date.	Urine.							Faeces.		Weight. Gms.	Notes.
	Amt. c.c.	Sp. Gr.	Total N Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Total N. Gms.	Per Cent. N.		
Control Period.											
Oct. 21	525	1013	6.84	5.67	82.9	0.323	4.7	0.1285	3.0	13,780	
22	430	1017	6.45	5.35	83.0	0.320	4.9	0.1285	3.0	13,860	
23	545	1012	6.65	5.46	82.1	0.318	4.8	0.1285	3.0	13,840	
24	½ right kidney removed—wt. 25 gms.										
26	430	1016	8.25	7.09	86.0	0.338	4.1	0.1894	4.2	13,410	Albuminuria
27	430	1018	7.22	6.04	83.4	0.315	4.4	0.1894	4.2	13,400	
28	480	1014	7.81	6.53	83.5	0.293	3.8	0.1894	4.2	13,240	
Nov. 4	325	1020	6.69	5.62	85.5	0.231	3.5	0.2641	4.4	13,500	
5	440	1017	6.56	5.60	86.5	0.286	4.3	0.2641	4.4	13,770	Diarrhoea
6	430	1016	6.26	5.18	82.9	0.266	4.2	0.2641	4.4	13,610	
7	325	1018	5.25	4.34	82.6	0.240	4.6	0.2641	4.4	13,760	
8	460	1015	5.9	4.87	82.5	0.321	5.4	0.2641	4.4	13,840	Diarrhoea
8	½ left kidney removed—wt. 22 gms.										
20	410	1012	5.89	4.93	83.6	0.264	4.5	0.1765	3.07	11,810	
21	440	1013	5.65	4.83	85.6	0.291	5.1	0.1765	3.07	11,960	
22	510	1010	5.52	lost.		lost.		0.1765	3.07	11,930	100 c.c. extra water
Dec. 3	725	1008	7.14	6.14	85.9	0.343	4.8	0.6335 (?)	4.68	12,250	300 c.c. extra water
4	615	1009	6.39	5.31	83.1	0.298	4.7	0.6335 (?)	4.68	12,285	"
4	3d operation—death in 3 hours. Oedema of lungs.										

Weight of kidney removed at first and second operations..	47 gms.
Weight of kidney found at autopsy......................	43.7 gms.

was extirpated and in the case of the former the remaining half of this kidney was taken out at a third operation. In some instances one entire kidney and half the opposite kidney were removed at one operation without any immediate ill effect. The present work includes metabolism studies on four dogs with varying degrees of kidney reduction, but a somewhat exhaustive study of the general effects of extirpation and of the process of repair in the kidney after various kinds of operative injury will be published later by Dr. J. A. Sampson and myself. At present it is sufficient to state that we have had no difficulty in keeping animals alive and in good condition without either general or local disturbances after

TABLE II.

(Dog 21, ⅔ reduction.)

Date.	Urine.							Faeces.		Weight Grams.
	Amount c.c.	Sp. Gr.	Total N. Grams.	Urea. Gms.	Urea. Per Cent.	Ammonia Gms.	Ammonia Per Cent.	Total N. Grams.	Per Cent. N.	
Dec. 3	Rt. kidney (wt. 29 gms.) $\frac{1}{3}$ Lt. kidney (wt. 10 gms.) } Removed									8,410
17	440	1014	6.47	5.59	86.4	0.282	4.4	0.1806	4.34	8,210
18	437	1014	6.18	5.70	83.7	0.269	4.4	0.1806	4.34	8,230
19	435	1015	5.24	4.28	81.7	0.259	4.9	0.1806	4.34	8,225
Jan. 6	Killed									8,050

Weight of kidney removed at single operation........	39 gms.
Weight of kidney remaining at autopsy..............	16.5 gms.
Total weight	55.5 gms.

TABLE III.

(Dog 12, spontaneous nephritis, unilateral nephrectomy.)

Date.	Urine.							Faeces.		Weight Gms.	Notes.
	Amt. c.c.	Sp. Gr.	Total N. Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Total N. Gms.	Per Cent. N.		
Nov. 16	250	1031	6.55	5.04	77.2	0.276	4.2	0.1514	2.93	17,820	Alb. 4% Casts +++
18	300	1028	6.71	5.39	80.4	0.290	4.3	0.1514	2.93	17,610	
19	212	1036	6.42	4.99	77.8	0.345	5.3	0.1514	2.93	17,520	
20	260	1034	6.66	5.22	78.4	0.362	5.4	0.1514	2.93	17,500	
22											Alb. 2½% Casts +++
Dec. 6	Right kidney removed, weight 72 gms.							0.2058	3.58		
10								0.1981	3.44		Alb. 1½% Casts ++
11	405	1017	7.80	6.05	77.6	0.335	4.29	0.1981	3.44	17,110	300 c.c. extra water
12	505	1015	6.44	5.23	81.1	0.313	4.86	0.2108	3.59	17,100	300 c.c. extra water
16								0.2108	3.59		
20	Died during operation on other kidney, which weighed 68 gms.									16,650	

the removal of one-quarter, one-half, and in some instances three-quarters of the total kidney substance at one operation. The removal of larger amounts and occasionally of three-quarters is followed by severe general disturbances which have rendered futile all attempts to maintain the animal in nitrogenous equilibrium. In one instance after removal of a considerable portion of the kidney substance, a nephritis developed, which added to the value of the experiment rather than otherwise.

TABLE IV.

(*Dog* 13, 3/4 *and* 6/7 *reduction; acute nephritis.*)

Date.	Urine.							Faeces.		Weight Gms.
	Amount c.c.	Sp. Gr.	Total N. Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Total N. Gms.	Per Cent. N.	
Nov. 2	Half left kidney removed, weight 14.5 gms.									15,840
13	Entire right kidney removed, weight 42 gms.									14,000
16	Nephritis. Alb.=½ per cent. Abundant casts.							0.2125	5.53	13,100
21	410	1011	5.72	5.29	(?) 92.5	0.166	2.9			12,970
22	320	1016	4.78	4.84	80.2	0.251	5.2			13,070
23	375	1019	5.40	4.62	85.3	0.272	5.2			13,270
Dec. 3-8	Does not eat—more or less vomiting									
6	267	1016	3.61	2.87	79.5	0.143	4.0	0.0990	5.74	12,680
7	222	1020	3.04	2.43	79.9	0.119	3.9	0.0990	5.74	12,590
9	Eight gms. of remainder of left kidney removed.									
10-20	Gastro-intestinal disturbance—does not eat. Alb, 1½-2 per cent. Casts abundant.									
16								0.1766	6.66	
18	165	1016	1.89	1.56	82.5	0.040	2.1	0.0557	6.65	10,350
19	120	1017	1.47	1.24	84.4	0.028	1.2	0.0557	6.65	10,200
20	195	1008	0.689	0.437	63.4	0.527	7.6	0.0557	6.65	10,000
21	Chloroformed.									

Weight of kidney substance removed	64.5 gms.
Weight of remaining kidney	11 gms.
Total weight	75.5 gms.

The results are shown in Tables I, II, III and IV. As a normal control period is given in one experiment only (Table I) a series of controls[8] are presented in Table V. These give the figures in six dogs fed on the same diet and kept under the same conditions as the dogs with kidney reduction. The averages only are given and are based on the figures of periods of three to five successive days.

Experiment I shows no appreciable changes in metabolism after the removal of one-half of one kidney or one-half of each kidney. The animal unfortunately died a few hours after the

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[8] Taken from paper by Pearce, R. M., and Jackson, H. C., Experimental Liver Necrosis; III, Nitrogenous Metabolism, *Jour. Exper. Med.*, 1907, ix, 552.

TABLE V.

Normal Dogs—Control.

Dog.	Total N. Gms.	Urea.		Ammonia.		Creatinin.		Undetermined N.		Average of
		Gms.	Per Cent.	Gms.	Per Cent.	Gms.	Per Cent.	Gms.	Per Cent.	
A	6.35	4.96	78.1	0.019	7.9	0.606	9.5	0.259	4.1	Five 24° periods.
B	3.30	3.24	86.1	0.128	3.3	0.278	7.4	0.108	2.9	Four " "
C	4.10	3.98	78.4	0.450	8.8	0.350	6.7	0.326	6.0	Four " "
D	7.04	5.39	81.2	0.395	5.5	0.345	4.8	0.568	8.1	Three " "
E	6.56	5.30	80.7	0.428	5.8	0.281	4.2	0.537	7.9	Three " "
F	6.57	5.61	85.3	0.364	5.5	0.354	5.4	0.213	3.4	Three " "
G	5.36	4.34	82.0	0.332	6.7	0.208	3.9	0.377	7.4	Four " "
Average Per Cent.			81.7		6.2		6.0		5.7	

third operation with no lesions discoverable at autopsy except a very extensive edema of the lungs.

Experiment II indicates that the removal of two-thirds of the entire kidney substance at one operation does not interfere with the general condition of the animal as shown by the constant weight and normal metabolism figures.

The third experiment made on an animal with a spontaneous nephritis, a condition occasionally found in stray dogs, shows that this lesion has no effect on metabolism, even after the kidney substance is reduced one-half by a unilateral nephrectomy.

The fourth experiment was not planned for a study of metabolism, but when it was found that an animal with but one-quarter of its kidney substance had developed an acute nephritis, thus diminishing, it was assumed, the functional capacity of the fractional portion of the kidney remaining, it seemed too good an opportunity to lose and the animal was placed on a constant diet and the metabolism experiments carried out six days later. This animal, despite the great reduction of kidney substance and the presence of a nephritis, had a normal metabolism during the first three day observation period. Two weeks later, however, when appetite had begun to fail equilibrium was lost, although no change in the percentage relations of nitrogen was evident.

But after another period of two weeks had elapsed, and the kidney substance had still further been reduced by operation, leaving the animal with but one-seventh of its original kidney material, a change in the urea-ammonia ratio, indicative of inanition, occurred. That this final change is due, as Bainbridge and Beddard claim, to inanition there can be no doubt. Up to this point, the beginning of starvation, the changes in urea described by Bradford were not observed.

The discrepancy between these results and those of Bradford require a word of comment. Bradford, it will be remembered, found an increase of urea to occur with considerable frequency after removal of one-half or two-thirds of the kidney substance and almost constantly after removal of three-fourths. In the experiments here quoted the urea remained constant until the period of inanition. In my experiments exact twenty-four-hour samples of urine were obtained by catheterization, the animals were kept on a constant diet (casein, lard, cracker dust) and the more exact Mörner-Sjoquist method for the determination of urea was used. Bradford's estimations on the other hand were based on the amount of urine voided naturally in twenty-four hours; the diet (meat and biscuit) was weighed accurately but was administered according to the appetite of the animal; and the urea was estimated by the relatively inaccurate hypobromite method. The differences in methods explain, I think, the variance in results.

Creatinin estimations were not made in these experiments on account of the negative results obtained by Bainbridge and Beddard. The undetermined nitrogen was therefore not calculated, but if the averages for creatinin in normal dogs, presented in Table V, are taken as indicating the probable creatinin excretion and added to the urea and ammonia percentage it is found that the undetermined nitrogen does not in any instance, except in the dog with spontaneous nephritis (Table III) and in the later period of Dog 13 (Table IV), vary widely from the normal average of five and seven-tenths per cent. In this regard the nitrogen determination would therefore also appear to be normal. As far as the urine is concerned it would appear that no evidence is at hand to indicate that the kidney, through an internal secretion or otherwise, has any influence on general nitrogenous metabolism and I believe the theory of internal secretion in this regard at least may be set aside. There remains, however, the very important question of why the removal of more than three-fourths of the kidney substance leads to loss of appetite and consequent inanition. Although vomiting occasionally occurred in these animals it did not seem to be sufficiently frequent or severe to indicate a general gastro-intestinal disturbance. To test this point extirpation of the kidney was done on two dogs after the establishment of a gastric fistula. In this way it was hoped that the food necessary for nitrogenous equilibrium could be introduced artificially and by examination of both urine and feces some light might be thrown on the cause of the disturbance. These efforts were rendered futile, however, by the inability of the stomach to retain the materials introducd. The conclusion is inevitable therefore that although the kidney appears to have no direct influence on nitrogenous metabolism the removal of large portions of its substance does indirectly lead to disturbances of general nutrition by interfering apparently with the functions of the alimentary canal.

Examination of the Feces. The occurrence of serious gastric and intestinal disturbances in these animals after kidney reduction and their general similiarity to lesions occurring occasionally in man in the course of chronic nephritis led me, in view of our more recent ideas of the chemical control of the body and the influence of one secretion on another, so well brought out by Starling and Baylis's investigations, to study the feces of the animals in order to determine if partial nephrectomy had any influence on digestion, absorption or elimination into the intestine. Brainbridge and Beddard's claim that the disturbance in metabolism is due to inanition dependent on vomiting and diarrhea with eventual failure to take food and not to a direct influence of the kidney dodges the question. The point to be determined is whether or not the gastric and intestinal disturbances are caused by faulty absorption or by digestive disturbances due to the elimination into the intestine of products normally removed by the kidneys. The demonstration of such a relation would be important not only as an illustration of the chemical interrelationship between various organs, but would also aid in explaining similar disturbances associated with the nephritis of man.

These latter which, I understtand, are frequently so severe as to present symptoms closely resembling a violent gastroenteritis have been ascribed in part to alterations of the mucosa due to edema, and in part to the influence of the uremic condition on the central nervous system. While these explanations account for many of the symptoms, others, according to von Noorden,[9] must be attributed to toxic chemical action. In fact recent investigations show that in uremia substances usually eliminated by the kidneys are secreted vicariously into the alimentary tract. "Of these, the most irritating chemically is ammonia, which is formed in the intestine by decomposition of the secreted urea. It is also noticeable that the feces in uremic diarrhea are extremely rich in ammonia."

Studies of the feces having for their object the determination of the degree of absorption in nephritis, for which we are indebted mainly to von Noorden, show that the absorption of fats is very complete. The situation in regard to nitrogen is not so clear, the loss in some cases being greater than normal while in others an abnormally high percentage is found. The variation in some individuals, without a corresponding change in diet, or in the nature of the stools, or in the general condition and with no change in the percentage of dry substances or fat content of the feces, led von Noorden to the conclusion that the increase of nitrogen was due not to impaired absorption, but to the vicarious excretion of metabolites stored up in the organism. In many cases the excretion remained normal. High amounts, above three grams daily, were found in nephritis only in diarrhea (uremic) and were due largely to a high content of ammonium salts, constituting sometimes ten to twenty per cent. of the total fecal nitrogen.

In the four experiments tabulated above the total nitrogen in the feces evacuated during control periods and periods of metabolism study was estimated. The results as seen in the tables indicate no marked change in the total nitrogen or its percentage relation, except possibly in Experiment IV. In this animal with but one-seventh of its kidney substance, which after the first operation developed a severe nephritis, the *percentage* of nitrogen in the feces apparently shows a somewhat marked increase as compared with the other dogs. Unfortunately, no control figures on this animal are at hand. The low total nitrogen combined with a high percentage would appear to indicate the presence of substances of a higher nitrogen percentage content (*e. g.*, ammonia) than those normally present in the feces. This phase of the problem will be further investigated.

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[9] Von Noorden, C., Metabolism and Practical Medicine (Vol. ii). Chicago, 1907.

The inanition due to gastro-intestinal disturbance cannot therefore be explained by impaired absorption, or, except as possibly indicated by Experiment IV, by an undue elimination of nitrogenous substances. Irritation by increased elimination of toxic substances, non-nitrogenous in nature, may be a factor, but upon this point I have as yet no observations.

CONCLUSIONS.

1. The removal of one-half, two-thirds and sometimes three-quarters of the kidney substance in the dog causes no change in the general nitrogenous metabolism as determined by estimations of the total nitrogen, urea and ammonia elimination by the urine.

2. The removal of larger amounts, and sometimes of three quarters of the substance, leads to the metabolism condition of starvation. This, however, is apparently the result of the gastro-intestinal disturbance constantly associated with extensive kidney reduction and not of a disturbance of general nitrogenous metabolism.

3. The determination of the amount of fecal nitrogen indicates that the gastro-intestinal disturbance is not due to diminished absorption; and except in one instance there was no evidence of its being due to an increased elimination of nitrogenous substances into the intestine.

4. These experiments do not support the theory that the kidney furnishes an internal secretion having an important influence on general nitrogenous metabolism. At least, if such a function exists, it is not disturbed by the removal of three-quarters of the kidney substance.

5. The metabolism in excessive kidney reduction is that of inanition dependent on gastro-intestinal disturbances presumably due to faulty chemical correlation. In this connection further knowledge concerning the elimination into the intestines of toxic substances is desirable.

CONCERNING THE PRESENCE OF NEPHROTOXIC SUBSTANCES IN THE SERUM OF ANIMALS WITH EXPERIMENTAL NEPHRITIS.*

By RICHARD M. PEARCE, M. D.
AND
H. P. SAWYER, M. D.

During the period of the active investigation of cytotoxic immune sera many attempts were made to utilize the results of the study of nephrotoxic sera in the explanation of various complications of chronic renal disease. It was assumed that if the injection into an animal of kidney parenchyma caused the appearance in the serum of that animal of a substance toxic, upon injection, for the kidney of another animal (heteronephrotoxin) it should be possible also to produce toxic substances in the serum of the same animal by so injuring its kidney as to cause degeneration of the renal cells. The production of such a serum (autonephrotoxin) by injuring one kidney, as by ligation of ureter, vessels, or entire pedicle, was attempted by several investigators, who claimed to be able to thus produce histological changes in the opposite kidney with the appearance of albumin in the urine. The serum of such animals also, it was claimed, had a similar effect if introduced into a normal animal of the same species (isonephrotoxin). Upon such experiments was based the theory that in chronic nephritis the continual degeneration of renal parenchyma was accompanied by an equally constant formation of autonephrolysin, the one dependent on the other, and that there was thus brought into play a vicious circle capable of explaining the course of this disease. Unfortunately for this and other theories based on similar observations, much of the early work on immune-cytotoxins, on account of faulty methods, has been discarded; the theory of specificity has been set aside, and the observation concerning the production of autonephrotoxin by experimental ligation cannot be confirmed.

There is, however, a phenomenon brought out by the investigations along this line which remains unexplained and

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* Work aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. of Med. Research*, 1908, xix, 269.

which is of peculiar interest in connection with any discussion of the pathology of nephritis. This is the observation of Lindemann[1] that the serum of an animal suffering from an experimental chromate nephritis has the power to produce lesions of the kidney when introduced into a normal animal and also my own[2] observation of similar results when the serum of dogs with spontaneous nephritis, or of those with lesions due to nephrotoxic serum, as had also been noted by Bierry,[3] are introduced into normal dogs. Such injections cause the excretion of albumin and casts and histological changes in the kidney. These observations which, as far as I am aware, have never been questioned, indicate the presence in the serum either of a substance formed anew during a nephritis or an accumulation of toxic substances (metabolites) normally eliminated by the kidney. The phenomenon is quite distinct from that of the action of a substance produced by immunization, as it represents presumably the action of a substance or substances resulting from tissue destruction, or faulty function, or both. If found to be a constant attribute of the serum of experimental nephritis it is a matter of extreme importance in connection with the pathology of chronic nephritis. We have, therefore, largely on account of the interest of one of us in various problems of chemical correlation as applied to the kidney[4] re-opened the subject in the hope of determining upon what factors the observation in question rests.

Methods. From the outset the object of our investigation has been not so much the accumulation of positive evidence in support of this phenomenon as a thorough control study of the possibilities of error. As we have taken the appearance of coagulable protein in the urine as the criterion of kidney injury, we have attempted to control every other possible source of such protein. For this reason and because the phenomenon has been frequently quoted and generally accepted by writers on diseases of the kidney we present our methods and results in considerable detail. As this study is largely a control investigation of a definite phenomenon and not of the methods of producing it, and as Bierry and Pearce are in accord concerning the action of the serum of an animal in which nephritis has been produced by a nephrotoxic immune serum, we have not repeated the experiments of the former, but have adopted, instead, Lindemann's simpler method of utilizing the serum of animals with chromate nephritis. A study has also been made of the effect of the serum of animals with uranium nephritis.

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[1] Lindemann, W. Ueber das Wesen der toxischen Nephritis. *Centralb. f. allg. Path. u. path. anat.*, 1900, xi, 308.

[2] Pearce, R. M. An experimental study of nephrotoxins. *Univ. of Penn. Bull.*, 1903, xvi, 217.

[3] Bierry, H. Recherches sur l'injection de sang et de sérums nephrotoxiques au chein. C. R. Acad. d. Sciences, 1901, cxxxii, 1145.

[4] Pearce, R. M. The theory of chemical correlation as applied to the pathology of the kidney. Annual Address before the Philadelphia Pathological Society, April 23, 1908.

The demonstration of the possible toxic action of a serum on the kidney has been attempted in two ways; first by the examination of the urine after the injection of the serum of animals with experimental nephritis and second, the action of such serum, in vitro, upon renal cells. Dogs and rabbits were used. In experiments of the first type the urine was examined for several days or a week for albumin and casts. This is very important in both dogs and rabbits, but especially in the former on account of the frequency of spontaneous chronic nephritis. The animals which were to furnish the serum received injections of either potassium chromate or bichromate or of uranium nitrate. The former were given subcutaneously to rabbits in doses .03 gram and to dogs .06 gram daily or every other day, and the latter in like manner in doses of .0075 gram to rabbits and .015 gram to dogs. An estimation of the degree of kidney injury was obtained by daily examination of the urine. The animals were bled from the femoral artery after periods varying from two to five days. The serum thus obtained was injected into normal animals, always of the same species, as soon as possible after bleeding, usually within two to four hours, though occasionally on account of the slow separation of the clot, the serum stood over night before being used. The injections into rabbits were made into the ear vein without anesthesia. Dogs received the serum either in the abdomen without anesthesia or, after incision of the skin, in a small subcutaneous vein opposite the second joint of the hind leg under light ether anesthesia.

In these experiments the presence of coagulable protein and of casts in the urine has been taken as evidence of an influence of the serum upon the kidney. All possibilities of contamination of the urine were avoided. The animals were kept in metabolism cages which were scrupulously cleaned daily and the food limited to dog biscuit, which could not readily become mixed with the urine. In those experiments with dogs in which the skin was incised before the injection the wound was carefully dressed in order to prevent oozing of blood or serum. Dogs developing a diarrhea, as occasionally happened, were discarded.

Owing to the almost constant presence of mucin in the dog's urine, as shown by Jackson and one of us[5] elsewhere, and the necessity of controlling this in the test for albumin, the following procedure was adopted: Four portions of absolutely clear filtered urine were placed in test-tubes; the first served as control, to the second acetic acid only was added, to the third acetic acid and potassium ferrocyanide solution ,and the fourth was heated and acetic acid then added. The amount of acid added to each tube was always the same and approximately the same quantity urine was used daily. By this method the clouding or precipitate due to mucin was, we think, accurately controlled. This clouding of normal dog's urine by the presence of mucin may be expressed thus 0, +, +, +. This we have taken as a normal standard and when clouding in both third and fourth tubes has been greater than that in the second we have considered it evidence of the presence of protein, and the degree of clouding we have indicated by multiplying plus signs.

The centrifugalized sediment of the urine has been examined with special regard to the presence of casts, renal cells, and red and white blood corpuscles.

Results. Eight dogs received the serum of dogs with chromate nephritis. Of these four were injected intravenously. In one, receiving the serum in dose of one cubic centimeter to five hundred and seventy-eight grams of body weight, no change in the urine occurred. In a second and a third, doses of one to four hundred and ninety-three and one to three hundred and fifty respectively, a trace of protein was present in the urine on the day following the injection. In the latter of these a few finer granular casts, renal cells, and leucocytes were found in the sediment. The fourth experiment is given in detail, as follows:

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[5] Pearce, R. M., and Jackson, H. C. Concerning the production of cytotoxic sera by the injection of nucleo-proteids. Jour. Infect. Dis., 1906, iii, 742.

Dog 61.—February 28, female, weighing fifteen thousand three hundred thirty grams, placed in metabolism cage.

February 29 to March 3, urine contains no albumin and sediment is negative.

March 3, received in small vein of leg under light ether anesthesia, thirty-two cubic centimeters (dose 1 to 480) of serum of chromate dog.

March 4, cage urine (seventy cubic centimeters, Sp. Gr. 1034) contains a considerable amount of coagulable protein which unfortunately was not estimated. Sediment shows numerous fine fat globules and cells of the type of renal cells and a few polymorphonuclear leucocytes; no casts, no red blood corpuscles. Urine from bladder at 11 a. m. amounts to seventy cubic centimeters with a specific gravity of 1020 and contains five-tenths per cent. protein by the Esbach method. Sediment contains numerous cells of renal type and a few leucocytes. Urine from bladder at 3 p. m., sixteen cubic centimeters in amount, Sp. Gr. 1034, protein two and five-tenths per cent., sediment unchanged.

March 5, cage urine amounts to one hundred fifty-four cubic centimeters, specific gravity is 1042 and Esbach method gives two and five-tenths per cent. protein; sediment as on the fourth. Urine from bladder at 9 a. m. contains but a trace of protein with elements of sediment fewer in number.

March 6, protein twenty-five hundredths per cent., sediment contains few renal and pus cells but no casts.

March 7, ditto.

March 8, urine, one hundred sixty-five cubic centimeters, specific gravity 1038, color amber, protein twenty-five hundredths per cent., sediment contains a small number of renal cells and leucocytes and fat globules and for the first time a few finely granudar casts.

March 9 and 10, protein and sediment as on the eighth.

March 11, two hundred and seventy-five cubic centimeters of urine, specific gravity 1029, protein in traces which cannot be estimated by Esbach. Sediment negative except for an occasional leucocyte.

March 12 to 15, urine normal. Weight of dog on March 15 fourteen thousand four hundred twenty grams.

In order to control the possible toxic action of ether on the kidney and also any accidental admixture of protein to the urine, by oozing of blood or serum from the incision over the injected vein, four dogs received serum injected directly into the peritoneal cavity without ether and without incision. The dose varied from one to two hundred and eighty-seven to one to four hundred and ninety. In all of these the injection was immediately followed by the appearance in the urine for a period of two to five days of traces of protein and small numbers of finely granular casts, but in none was the amount of protein equal to that in the urine of dog 61 previously described. The following experiment is typical of this group:

Dog 63.—February 28, male puppy, weighing four thousand nine hundred and seventy grams, placed in metabolism cage. February 29 to March 3, urine normal. Results of tests for protein give the mucin reaction (0, +, +, +). Sediment negative.

March 4, ten cubic centimeters of chromate serum (dose 1-490) injected into peritoneal cavity.

March 5, protein tests, 0, +, 3+, 3+; sediment; few renal cells and leucocytes; no casts.

March 6, protein tests ditto, sediment as above with addition of a few finely granular casts.

March 7, no urine.

March 8, as on sixth.

March 9, 10, and 11, urine normal.

It is worthy of note that the lesions produced were not as severe or as constant as those described by Lindemann.

The experiments with uranium serum include one dog injected intravenously and four intraperitoneally. The intravenous injection (dose 1:1000) was followed by an elimination of casts without albuminuria. The casts were present in small numbers and were of a finely granular type with an occasional hyaline or epithelial cast and a few renal and white blood cells. The casts appeared on the first and third days after injection and could not be found on the fourth and fifth days. Casts had not been present in the preliminary examination covering a period of six days.

On account of the peculiar result of this experiment the animal was injected intraperitoneally on the fifth day. The same serum, which had been kept on ice, was used (in the dose of 1:370). Casts of the finely granular and hyaline types and renal cells and leucocytes reappeared in the urine for two days, but no protein could be detected.

Of the three experiments in which uranium serum was injected intraperitoneally, one (dose 1:408) was negative and the other two (doses 1:400 and 1:635) showed a transient elimination of small amounts of coagulable protein with, in one, a few hyaline and finely granular casts and in the other no casts.

Although these experiments with dogs give a fair proportion of positive results, a small number of similar experiments with rabbits were absolutely negative. Three rabbits received uranium serum and two chromate serum in doses of five to twelve cubic centimeters (1:110 to 1:350) with no change whatever in the urine.

Although this investigation has to do mainly with the effect of the serum of experimental nephritis, the detection in the course of our routine examinations of several instances of spontaneous nephritis has permitted the testing of such serum. In an earlier communication, one of us[1] describes the occurrence of albuminuria with the elimination of casts in three of seven dogs receiving such serum intravenously. Of the present experiments, two in number, one confirms this earlier experience. The serum of a dog with spontaneous nephritis, eliminating from two to five per cent. protein and an abundance of casts throughout the month during which it was under observation had a definite nephrotoxic power (in the dose of 1:210). The serum of a second dog with a less severe nephritis had no effect in the same dose.

The occurrence of spontaneous nephritis in the rabbit was observed but once. An animal eliminating .5 to 1.25 per cent. protein daily was bled and its serum injected in doses of ten cubic centimeters (1:150) into two rabbits with no effect.

In three instances dogs with spontaneous nephritis were utilized in another way. It occurred to us that if the serum of an experimental nephritis has a toxic action on a normal kidney it might have the power to aggravate an existing spontaneous nephritis. One of these dogs therefore was injected, intravenously, with uranium serum (dose of 1:400) and a second with chromate serum, intraperitoneally (dose of 1:460), but without effect on the elimination of protein or casts. In a third experiment of this type a dog weighing nine thousand ten grams, with a very severe nephritis, received at the same time forty cubic centimeters of uranium serum, intravenously, and twenty cubic centimeters in the abdomen, without result.

A word may be said about another phase of this subject. Bierry and also Pearce have shown, apparently conclusively, that the serum of a dog suffering from a nephritis caused by a heteronephrotoxic serum (prepared by injecting the rabbit with dog's kidney) has a definite nephrotoxic power when injected into the blood stream of a second dog. We have not repeated these experiments, but in the course of our work on another problem we found it necessary to procure the reverse type of immune nephrotoxic serum, that is, one toxic for the rabbit's kidney (prepared by injecting rabbit's kidney into the dog). This serum had a definite toxic action on rabbit's kidney, but the serum of rabbits so treated when injected into normal rabbits (dose 1:100 to 1:200) had no nephrotoxic effect, as is the case in the dog.

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[1] Pearce, R. M., and Jackson, H. C., loc. cit.

It is noteworthy that by no method of experimentation have we been able to demonstrate a nephrotoxic action of the serum of rabbits with kidney injury.

The question arises as to whether the toxic action of the serum of an experimental nephritis in the dog may be due, not to some peculiar substance developing as the result of injury to kidney cells, but to metabolites retained as the result of imperfect kidney function. We have performed no experiments, such as the injection of the serum of animals with complete nephrectomy, to test this point, but have found that the serum of animals with experimental reductions of the kidney substance to one-fourth the normal amount has no effect on the kidney of normal dogs. This conclusion is based on experiments with the sera of two dogs, the serum of one obtained one month and of the other two months after extirpation of three-quarters of the kidney substance. Thirty cubic centimeters of the first serum was injected in a dog weighing five thousand four hundred forty grams and thirty-two of the latter in a dog six thousand grams in weight. In neither did protein or casts appear in the urine.

The power of the serum of experimental nephritis to agglutinate renal cells in vitro was tested with seven sera. A mixture of renal cells in salt solution was prepared from the washed kidney, and to one-half cubic centimeter lots in test-tubes were added five cubic centimeters of each of the sera to be tested. Cell mixtures and sera were used within a few hours after they were obtained. Observations were made every hour for six hours. As a control, normal dog serum was used. Three sera of dogs with uranium, three with chromate, and one with spontaneous nephritis were tested in this way. In no instance did agglutination occur, and the degree of precipitation did not differ from that of the control. No difference in cell structure could be detected by microscopic examination.

In so far as this method of testing may be of value these results point to the absence of an isonephrotoxic activity of the serum of experimental nephritis and the results are not in accord with those obtained by injecting the same sera into the living animal.

In addition to the various methods of control which we have described, there is naturally the question of the elimination by the kidney of an excess of protein injected into the blood stream. In view of the fact that the injections have always been made into an animal of the same species and also that the amounts injected have been comparatively small, this factor could be set aside at once if it were not for a curious observation of Weiss.[6] This investigator as the result of a very extensive series of experiments came to the conclusion that all foreign sera cause albuminuria of some degree, but that homologous sera do not except when the serum of one sex is injected into the opposite sex. His evidence on the latter point, however, rests on a single experiment in which traces of protein resulted from injecting the serum of a male into a female rabbit and his quotation of Favaret's single observation of a like result upon injecting the serum of a bitch into a dog. In our control experiments, we have kept this point in mind, but have not been able to confirm it. In the dog, injections of normal dog serum in doses as high as one to three hundred, and in the rabbit of normal rabbit serum in doses of one to one hundred and fifty have failed to produce albuminuria, irrespective of the sex of the animal furnishing or receiving the serum. As we have always used homologous sera, the toxic effect of an alien serum does not come into question.

We have also controlled the possibility of a periodic albuminuria in the dog. For this purpose four dogs were set aside, and the urine of each examined daily for periods of ten days to two weeks. In none was albuminuria found nor were casts present during this time. Each gave the mucin reaction but nothing more. During this period two of these dogs were etherized and small quantities of blood taken from the jugular vein without any effect on the urine. These latter served therefore as controls also of our operative procedure.

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[6] Weiss, O. Ueber die Wirkungen von Blutserum-injectionen im Blut. Arch. f. d. Ges. Phys., 1896, lxv, 215.

The possibility of carrying over in the serum minute amounts of the salts injected must be considered. Attempts to detect, by the usual tests, the presence of chrome and uranium salts in the filtrate of the serum concentrated after coagulation have failed. Such tests, however, are not very sensitive and it is possible that traces may have been present. If present, the amount must have been so minute that it seems very improbable that they could have anything to do with the lesion described. Certainly they appear to have had no effect in the experiments with rabbits, and on this evidence alone we feel justified in ruling out the possibility of carrying over these salts in the serum.

In addition to the various controls described, we have by careful selection and elimination ruled out the possibility of an admixture to the urine of protein substances from local inflammatory conditions, as balanitis in the dog, or lesions of the uterus or vagina in the bitch. The surface of the entire body as well as the mouth of each animal has also been carefully examined for lesions capable of allowing a discharge of blood or serum. As the food has been limited to dry dog biscuit and the cage carefully screened to prevent particles dropping into the collecting bottle, we believe the presence of protein from the food can be ruled out.

In short, we have investigated every possible source of error which suggested itself, but have been unable to explain the presence of albumin in the urine except by a toxic action of the serum on the kidney.

CONCLUSIONS.

The positive results here described confirm the observation of Lindemann, Bierry, and Pearce that the serum of dogs with various types of nephritis has a toxic action on the kidney manifested by the appearance, for a short time, of protein and casts in the urine.

A very complete series of control observations offer no explanation for the appearance of protein other than as the result of injury to the kidney.

It has not been possible to demonstrate a nephrotoxic power for the serum of rabbits with experimental nephritis and it is therefore manifestly improper to assume that this nephrotoxic power is a constant characteristic of the serum of all animals suffering from nephritis.

For this reason, although the phenomenon observed is suggestive and worthy of investigation on a larger scale, it should be utilized with caution in any theoretical explanation of the pathology of chronic nephritis.

A STUDY OF EXPERIMENTAL REDUCTION OF KIDNEY TISSUE WITH SPECIAL REFERENCE TO THE CHANGES IN THAT REMAINING.[1]

By JOHN A. SAMPSON, M. D.
AND
RICHARD M. PEARCE, M. D.

The following experiments in reduction of kidney tissue in dogs were undertaken in order that one of the writers might study the influence of such reduction on nitrogenous metabolism[2] and also for the purpose of determining the effect of this procedure on the remaining kidney tissue and upon the general condition of the animal.

The scanty literature of the subject may be briefly reviewed as follows:

The most extensive series of kidney reduction is that of Bradford.[3] The operative procedure of this investigator was to remove from the middle of the kidney, entering the pelvis, a wedged-shaped mass of kidney substance. This mass was equal to one-quarter to one-half of the entire kidney. After a variable period of time the entire opposite kidney was removed. In some instances a wedge was taken from each kidney and later the remaining tissue still further reduced. Of a total of thirty-three dogs, four died after the first operation and six at or shortly after the second operation. Of the twenty-three surviving the second operation, eight lived a considerable period of time and were killed in good health. The effect on the kidney of the first operation was usually atrophy of the organ. This occurred also if both kidneys were operated upon. After the second operation no serious disturbance of health occurred but a variable amount of wasting, usually transitory, was the rule.

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[1] Aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Exper. Med.*, 1908, x, 745.

[2] Pearce, R. M., The Influence of the Reduction of the Kidney Substance on Nitrogenous Metabolism, *Jour. of Exper. Med.*, 1908, x, 632.

[3] Bradford, J. R., The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, *Jour. of Physiol.*, 1899, xxiii, 415.

If two-thirds of the kidney was removed death usually followed while the loss of three-quarters rendered survival impossible, death occurring usually in one to six weeks, from asthenia and great wasting.

Bradford found that two grams of kidney tissue per kilo of body weight was sufficient for maintenance of life (normal ratio 6.7 grams). Tuffier[4] gives 1.5 grams, Paoli[5] states that one-half a kidney is necessary. The latter found the operation to be followed frequently by hypertrophy of the glandular epithelium, dilatation of the vessel and a new formation of glomeruli and tubules. Tuffier's operation differed from Bradford in that he removed one entire kidney first and later a portion of the other. As a result of ten experiments he found no permanent disturbance of the urine and no effect on the development of growing animals.

Von Haberer's[6] experiments on three goats and thirty-eight dogs are most unsatisfactory because many of his animals died of pneumonia. He practiced very extensive resections within very short periods of time and showed that it is possible for a dog to survive the removal of one kidney and one-third of the other at a single operation or one and a half at two operations within a week. The mortality was very high.

Passler and Heineke[7] in their work on experimental heart hypertrophy, practiced extreme kidney reduction; they followed Bradford's method, allowing an interval of four weeks between the first and second operation; in five dogs cachexia and death followed. In eighteen surviving the second operation, at intervals varying from a few days to eleven months, a third, fourth, fifth or sixth operation was done, at each a small portion of kidney substance being removed. All finally died, from operations, accident or cachexia. As their interest was chiefly in heart hypertrophy, the details of the effect of reduction on the kidney tissue remaining are not given.

Bainbridge and Beddard,[8] working with cats according to Bradford's method, reduced the kidney substance three-quarters. This caused loss of appetite, wasting and death in a few days or weeks. Descriptions of the effect on the remaining kidney tissue are not given.

METHODS.

As our operative procedure differed from that of the other investigators it is here given in detail. If only one kidney was operated upon, it was exposed through a so-called "gridiron" incision in the lumbar region by separating the muscle fibers and not cutting them. If both kidneys were exposed at one operation, this was done transperitoneally through a median abdominal incision. In the first few experiments the pedicle of the kidney was compressed by an assistant while the upper pole was excised and then the bleeding was controlled by mattress sutures of catgut and silk passing through the entire kidney substance and the upper portion of the pelvis. Later it was found easier to place catgut sutures first as shown in Figs. 1 and 2, tie them and excise the upper pole, the operation usually being bloodless, and possible without an assistant.

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[4] Tuffier, T., Etudes expérimentales sur la chirurgie du rein, Paris, 1899 (quoted by Bradford).

[5] Paoli, Della resezione del rene *Cent. f. Chirurgie*, 1892, xix, 78.

[6] V. Haberer, H., Experimentelle Untersuchungen über Nierenreduktion und Funktion des restierenden Parenchyms, *Mitteilungen a.d. Grenzgebieten d. Med. u. Chir.*, 1907, xvii, 57.

[7] Passler and Heineke, Versuche zur Pathologie des Morbus Brightii, *Verhandl. d. Deutsch. path. Gesellsch.*, 1905, ix, 99.

[8] Bainbridge, F. A., and Beddard, A. P., The Relation of the Kidney to Metabolism *Proc. of the Royal Soc.*, B, 1907, lxxix, 75.

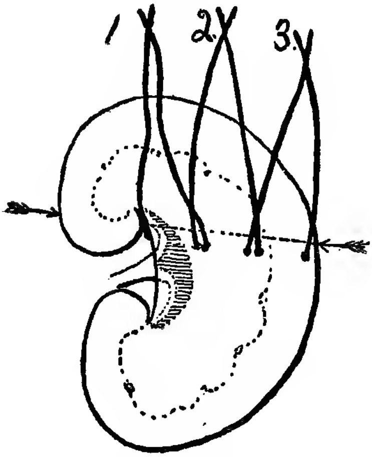

Fig. 1

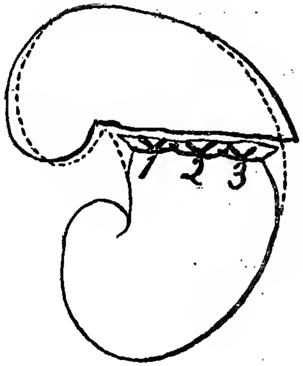

Fig. 2

FIG. 1. Technique of resection of upper pole of the kidney.

By means of a straight needle with a dull point, three interlacing mattress catgut (No. 2 Cumal) sutures (1, 2 and 3) are first passed through the kidney in a line which approximately divides the kidney in half (see illustration). Care must be taken to avoid injuring the ureter and for this reason the line of sutures is taken a little obliquely rather than straight across the kidney. These sutures are then tied, thus completely shutting off the blood supply to the upper pole. The upper pole is cut off from two to four millimeters beyond the sutures as indicated by the arrows.

FIG. 2. Immediate result of resection of upper pole of the kidney.

The dotted line indicates the original outline of the upper pole. After excising it, the base of the upper pole flares apart and the segment is thus lower and wider than before the operation. The sutures 1, 2 and 3 have been tied, thus constricting the upper portion of the remaining kidney tissue and by making the capsule more tense the part of the kidney, left behind, is a trifle smaller than before the operation.

This operative procedure we have considered preferable to that of Bradford and other investigators because there is a minimum disturbance of the blood supply of the kidney tissue remaining. The infarcted tissue, which results from the injury, and must be absorbed, lies at one pole of an otherwise intact kidney while in the experiments of Bradford and others, it is centrally located and thus possibly disturbs the nutrition of the entire organ. Our method furthermore permits of a more accurate estimation of the amount of kidney reduction in that the degree of reduction is represented by the part excised plus that outside of and that in the immediate neighborhood of the sutures. Histological examinations of kidneys from animals dying shortly after operation have shown that the zone of necrosis rarely extends more than one-half centimeter from the sutures into the remaining kidney tissue. By the other method, after the removal of a wedge-shaped piece of tissue from the midst of the organ, the sutures necessary to approximate the parts remaining and to control bleeding of necessity destroy a mass of kidney tissue which in proportion to that excised must be much greater than that destroyed in removing one pole. By our method a portion of the pelvis is necessarily removed and there is some danger of interfering with the flow of urine into the ureter. By proper care we have found that this can be avoided.

Except for the animals used for the metabolism studies above mentioned, the dogs were fed on dog biscuits, and did not have any exercise other than that possible in fairly roomy cages. The general condition of the animals was determined by observations in regard to appetite and weight.

All material obtained at operation or autopsy was preserved in ten per cent. formalin. No subdivisions of this material were made but large sections were obtained which represented the entire mass. By this method it was possible to study in one section, cortex, pyramid, pelvis and reparative or other changes in the field of operation. By superimposing these large sections it was possible to compare directly the remaining kidney tissue with that removed at operation and also to make tracings for comparison and illustrations.

Our experiments are sixteen in number, of which two (one death from anesthesia and another from hemorrhage shortly after operation) are excluded. The remaining fourteen experiments are divided into four groups.

Group I. Removal of Upper Pole of One Kidney.

No. 1 (Dog 40).

Operative Procedure.—January 23, 1908. Under ether narcosis, the upper pole of the left kidney was removed as shown in Figs. 1 and 2. The length of the left kidney was five and six-tenths centimeters and the portion remaining outside of the sutures was two and seven-tenths centimeters. At the same time the right kidney was exposed and measured.

Termination.—Killed on the twenty-second day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 11,020 to 9,710 grams.

Effect on Remaining Kidney Tissue.—Slight but definite atrophy. Healing is perfect, the renal tissue, compressed by the sutures, is replaced by fibrous tissue except for a small area of infarcted tissue corresponding to vessels showing obliterated endarteritis. In the fibrous tissue adjacent to the pelvis there is a small area of new bone formation. Otherwise the renal tissue is normal. The opposite kidney is apparently unaffected by the operation.

No. 2 (Dog 41).

Operative Procedure.—January 23, 1908. Under ether narcosis, the upper pole of the left kidney was removed. The length of the left kidney was six centimeters and the portion remaining outside of the sutures was three centimeters. At the same time the right kidney was exposed and measured.

Termination.—Killed on the thirty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 13,610 to 10,960 grams. Four weeks after the operation the urine contained a considerable amount of coagulable protein with numerous finely granular and fatty casts, pus and epithelial cells (urine was not examined before operation).

Effect on Remaining Kidney Tissue.—Very slight if any atrophy. Healing is perfect except for a few areas of necrotic tissue near the pelvis. In the scar there is an area of calcified tubules. Pelvic epithelum is greatly thickened and penetrates the underlying scar tissue, forming alveolar masses of epithelial cells.

Otherwise the renal tissue is normal. Opposite kidney is apparently unaffected by the operation.

No. 3 (Dog 31).

Operative Procedure.—December 31, 1907. Under ether narcosis, the upper pole of the right kidney was removed. The length of the right kidney was six and two-tenths centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters. At the same time the right kidney was measured.

Termination.—Killed on the forty-eighth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 10,620 to 9,650 grams. Urine, on the fourth day, was normal but at the time of autopsy contained coagulable protein and pus cells, but no casts.

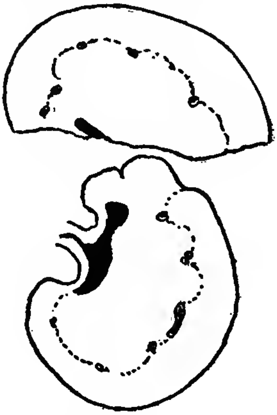

Fig. 3

FIG. 3. Tracings of sagittal sections of portions of a kidney, one portion removed at operation and the other at autopsy on the thirty-fifth day.

The upper pole was removed at operation as indicated in Figs. 1 and 2 and shows the characteristic flaring apart of the segment removed. The lower portion was removed at autopsy and has apparently atrophied but, by comparing it with a similar tracing of the opposite kidney and even from the measurements taken at the close of the operation (see Fig. 2), there is very little if any atrophy except in the tissue destroyed by the sutures and replaced by scar tissue. For description of microscopical findings see Experiment No. 2.

Effect on Remaining Kidney Tissue.—Very slight if any atrophy exists. Healing is perfect. There is dilatation of the pelvis of the kidney with a chronic pyelitis and thickening of the epithelium, and extensive bone formation immediately beneath this epithelium. Calcified tubules are present in the scar tissue. Otherwise the renal tissue shows atrophy of glomeruli with fibrous thickening of Bowman's capsule and extensive round cell infiltration of both cortex and pyramid. The tubules in places are dilated and in other places compressed. The portion of kidney removed at operation and the opposite kidney shows a spontaneous chronic nephritis but less marked than that just described.

GROUP II. REMOVAL OF UPPER POLE OF EACH KIDNEY AT ONE OPERATION.

No. 4 (Dog 65).

Operative Procedure.—March 7, 1908. Under ether narcosis, the upper pole of each kidney was removed. The length of the right kidney was four and five-tenths centimeters and the portion remaining outside of the sutures was two and three-tenths centimeters. The length of the left kidney was four and four-tenths centimeters and the portion remaining outside of the sutures was two and six-tenths centimeters.

Termination.—Died on thirtieth day.

General Effect.—Post-operative history was uneventful until the last week, when the animal refused food, lost weight rapidly and died on the thirtieth day.

Effect on Remaining Kidney Tissue.—No change in the size of the portion of the right kidney remaining. Healing was perfect except for a small area of necrosis along the line of suture, thickening of epithelium of pelvis and isolated masses of proliferating epithelium in the scar tissue. Otherwise the remaining renal tissue is normal.

The pelvis of the left kidney is filled with calculi, one occluding the lumen of the ureter. Associated with this there is an ulcerative pyelitis with abscesses involving the pelvic fat and lower portion of the pyramid. Where pelvic epithelium is intact it shows hyperplasia. There is no definite atrophy of cortex and pyramid.

No. 5 (Dog 66).

Operative Procedure.—March 7, 1908. Under ether narcosis, the upper pole of each kidney was removed. The length of the right kidney was four and nine-tenths centimeters and the portion remaining outside of the sutures was three centimeters.

The length of the left kidney was four and eighth-tenths centimeters and the portion remaining outside of the sutures was two and six-tenths centimeters.

Termination.—Killed on the fifty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 4,620 to 4,340 grams.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the right kidney remaining. Healing is perfect. There is moderate thickening of the epithelium of the pelvis. Renal tissue is normal.

There is no change in the size of the portion of the left kidney remaining, and it is similar to the right kidney.

No. 6 (Dog 1).

Operative Procedure.—May 23, 1907. Under ether narcosis the upper pole of each kidney was removed. The length of each kidney was six centimeters and the portion remaining outside of the sutures was three centimeters. Weight of portion of right kidney removed was ten grams and of left eleven grams.

Termination.—Died on one hundredth and sixty-fourth day, from general peritonitis, the fifth day after the removal of the remaining portion of the left kidney when the peritoneal cavity was opened and soiled with infected urine.

General Effect.—Post-operative history was uneventful. The dog was in the country during the summer and became pregnant. The weight at the time of the first operation was 13,180 grams; at the second operation (pregnant) 16,010 grams and after death with the uterus empty (aborted just before death) it was 12,110 grams.

Effect on Remaining Kidney Tissue.—Left kidney weighed eighteen grams, length four and eight-tenths centimeters, an increase of one and eight-tenths centimeters. There was a small calculus in the pelvis about a silk suture. Healing is perfect, kidney has assumed its normal shape and except for the presence of a silk suture it would be difficult to distinguish it from a normal kidney. Microscopically there is evidence of pyelitis.

Right kidney weighed twenty-eight grams, length five and one-tenth centimeters, an increase of two and one-tenth centimeters above the portion remaining beyond the sutures at operation. Healing is perfect, microscopically renal tissue is normal. There is bone formation beneath the epithelium of the pelvis.

GROUP III. REMOVAL OF ONE KIDNEY AND UPPER POLE OF THE OTHER AT ONE OPERATION.

No. 7 (Dog 35).

Operative Procedure.—January 23, 1908. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six centimeters and the portion remaining outside of the sutures was three and two-tenths centimeters.

Termination.—Killed on the sixth day (dying).

General Effect.—There was persistent vomiting after operation with gradual loss of strength, and failure to eat; a small amount of urine was passed daily.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney remaining. Extensive areas of infarction about the sutures are present with widespread calcification of the tubules. Infarcted area is one and five-tenths centimeters wide, the line of sutures being in the middle of this area. Abscess formation present about sutures.

No. 8 (Dog 69).

Operative Procedure.—April 6, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was five and seven-tenths centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters.

Termination.—Killed on the seventh day (dying). Cause of death not apparent.

General Effect.—Refused food and vomited persistently until killed on the seventh day. There was a loss of weight from 9,710 to 9,620 grams. Urine was voided after operation but was not examined.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. The area of infarction and hemorrhage is one and seven-tenths centimeters broad, the line of sutures being in the middle of this area. Very slight leucocytic infiltration about the sutures is present. There is marked proliferation of the pelvic epithelium.

No. 9 (Dog 24).

Operative Procedure.—December 9, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six and three-tenths centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters.

Termination.—Died on the tenth day.

General Effect.—Ate poorly, lost 500 grams in the first five days after the operation, hematuria.

Effect on Remaining Kidney Tissue.—There is no change in the size of the remaining portion of the left kidney. Infarcted area varies from one to one and three-tenths centimeters, the sutures being nearly at the junction of the normal and necrotic tissue. Otherwise the kidney is normal.

No. 10 (Dog 21).

Operative Procedure.—December 3, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left was five and two-tenths centimeters and the portion remaining outside of the sutures was less than half the original length of the kidney.

Termination.—Killed on the thirty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 8,410 to 8,050 grams. Slight albuminuria and pyuria.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect; a few calcified tubules are present in the scar tissue. Otherwise kidney tissue is normal.

No. 11 (Dog 72).

Operative Procedure.—March 21, 1908. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six centimeters and the portion outside of the sutures was three and two-tenths centimeters.

Termination.—Killed on the forty-first day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 15,060 to 12,340 grams. Urine obtained from bladder at autopsy was normal.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect; there are a few calcified tubules in the scar tissue. As compared with portion excised at operation and the opposite kidney there is no change in the renal tissue. Each show a chronic process characterized by round cell infiltration.

No. 12 (Dog 71).

Operative Procedure.—March 21, 1908. Under ether narcosis, the right kidney was removed and the upper pole of the left. The length of the left kidney was five and four-tenths centimeters and the portion remaining outside of the sutures was three centimeters.

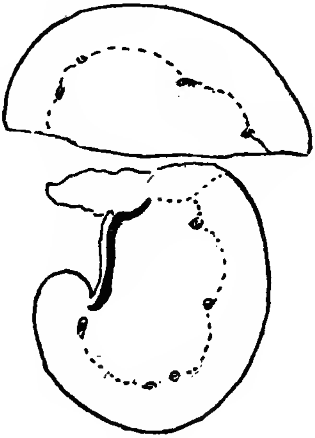

Fig. 4

FIG. 4. Tracings of sagittal sections of portions of a kidney, one portion removed at operation and the other at autopsy on the forty-first day.

For description of gross appearance see Fig. 3 and for description of microscopical findings see Experiment No. 11.

Termination.—Killed on the fifty-seventh day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 8,010 to 6,060 grams.

Effect of Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect, there are a few calcified tubules in the scar tissue, as in No. 11.

GROUP IV. REDUCTION OF KIDNEY TISSUE BY MULTIPLE OPERATIONS.

No. 13 (Dog 4).

Operative Procedure.—October 24, 1908. Under ether narcosis the upper pole (over $\frac{1}{2}$ approximately $\frac{5}{8}$) of the right kidney was removed. November 8, 1908. The upper pole of the left was removed. The length of the left kidney was six and five-tenths centimeters and the portion remaining outside of the sutures was three centimeters. December 11, 1908. The remainder of the left kidney was removed.

Termination.—Died four hours after the last operation from œdema of the lungs.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 13,826 to 12,250 grams and there were periodic albuminuria and pus cells.

Effect on Remaining Kidney Tissue.—There is slight if any atrophy of remaining portion of right kidney. Healing is perfect. A cheesy material containing calculi is present in the pelvis; bone formation in scar tissue beneath the pelvic epithelium; marked hyperplasia of pelvic epithelium. Kidney tissue is normal except for areas of round cell infiltration, also present in portion excised at first operation.

No change in the size of the remaining portion of the left kidney. Healing is perfect with extensive bone formation beneath the pelvic epithelium. In the pelvic fat there is a small abscess about one of the sutures. Otherwise tissue is as in the opposite kidney.

No. 14 (Dog 13).

Operative Procedure.—November 2, 1907. Under ether narcosis the upper pole of the left kidney (weight fourteen and five-tenths grams) was removed. The length of the left kidney was six and two-tenths centimeters and the portion remaining outside of the sutures was two and seven-tenths centimeters. November 13, 1907. The right kidney was removed (weight forty-two grams). December 9, 1907. A segment one centimeter thick was removed (weight eight grams) from the lower pole ot the remaining portion of the left kidney.

Termination.—Died eleven days after the last operation.

General Effect.—Good recovery from each operation except the last. More or less vomiting after the last operation, albuminuria one half to two per cent., abundant casts; voided urine until death and averaged 180 cubic centimeters for the last three days. There was a loss of weight from 15,840 to 10,000 grams.

Effect on Remaining Kidney Tissue.—The portion of the left kidney found at autopsy showed distinct atrophy and weighed eleven grams. Based on the weight of the normal right kidney this represents fourteen per cent. of the original kidney tissue. Healing from the first operation is perfect and site of second operation is occupied by a mass of necrotic tissue extending into the pelvis and surrounded by purulent fluid. Microscopically there is evidence of an acute ulcerative pyelitis with slight pyelonephritis and extensive cast formation in the tubules. Otherwise kidney tissue is normal.

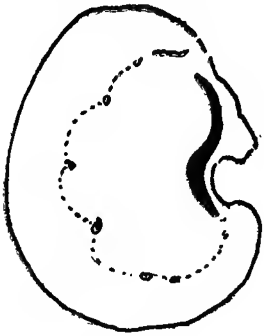

Fig. 5

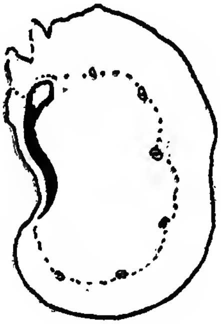

Fig. 6

FIG. 5. Tracing of sagittal section of portion of the right kidney remaining, 164 days after removal of the upper pole.

The upper pole was removed as indicated in Figs. 1 and 2.

The portion remaining shows distinct hypertrophy and the thickening of the cortex is most evident near the field of the operation. See Experiment No. 6.

FIG. 6. Tracing of sagittal section of the portion of the left kidney remaining, 159 days after removal of the upper pole.

The upper pole was removed as indicated in Figs. 1 and 2.

This is from the same dog as the kidney shown in Fig. 5 the hypertrophy is not as marked as in the other kidney but the thickening of the cortex near the field of operation is more marked and the kidney has almost resumed its normal contour. A calculus about a silk suture is present in the upper portion of the pelvis.

GENERAL SUMMARY.

The immediate effect of the operation on the portion of the kidney remaining is an infarction of the tissue compressed by the sutures. This area of necrosis extends but a short distance into the adjacent kidney tissue. The infarcted tissue gradually becomes replaced by fibrous tissue and in three to four weeks' time the necrotic tissue entirely disappears. The amount of fibrous tissue in time becomes so slight and the healing so perfect that it is difficult to detect the site of the operation. The renal elements sometimes persist in the infarcted area and the glomeruli apparently are more resistant than the tubules. The tubules in the infarcted area sometimes become calcified and bone formation beneath the epithelium of the pelvis is of very frequent occurrence. The pelvic epithelium usually shows marked proliferation and may invade the field of operation in alveolar masses. Calculi may form in the pelvis of the kidney. Sutures penetrating the pelvis as well as the necrotic tissue resulting from the compression of the sutures probably furnish the nuclei for the calculi.

Removal of approximately half of one kidney did not alter either the remaining portion of that kidney or the size of the opposite kidney in two animals of this series. These experiments were terminated on the thirty-fourth and forty-seventh days. In a similar experiment of twenty-one days' duration there was slight but definite atrophy of the remaining tissue of the kidney operated upon.

Removal of approximately half of each kidney at one operation did not alter the remaining kidney tissue in two animals of the second group. The longest period of observation was fifty-four days. On the other hand in a similar experiment where 164 days elapsed, the remaining portions of each kidney had increased markedly in size.

Removal of one kidney and approximately half of the other did not alter the remaining kidney tissue in six animals in which from five to fifty-six days elapsed before termination of the experiment.

In six experiments in which one kidney was removed and approximately half of the other, three of the animals died as a result of the operation on the sixth, seventh and tenth days. The probable cause of death was renal insufficiency; the animals refused food, vomited persistently and lost strength and weight. The other three animals recovered and were killed at periods varying from five to eight weeks. The reduction of the kidney tissue to one-quarter of its original amount at one operation was attained with danger but was not necessarily fatal.

In every experiment there was a loss of weight varying from four to twenty-four per cent. To what extent this loss in weight is due to the reduction of kidney substance and to what extent it is due to diet and confinement it is impossible to say, as we made no control experiments to elucidate these points.

THE RELATION OF LESIONS OF THE ADRENAL GLAND TO CHRONIC NEPHRITIS AND TO ARTERIOSCLEROSIS; AN ANATOMICAL STUDY.[1]

By Richard M. Pearce, M. D.

This investigation has for its object the determination, as far as may be possible by anatomical study, of the relation which exists between arteriosclerosis and changes in the adrenal gland on the one hand, and between chronic interstitial nephritis and adrenal lesions on the other.

The problem is of considerable general interest at the present moment in view of the numerous recent publications of French clinicians on this subject and has attracted my attention in connection with a recent critical study of the theory of chemical correlation as applied to the kidney.[2] It would appear natural, in view of our knowledge of the pressor effect of adrenalin and of the experimental lesions produced in the rabbit by this substance, as well as of our knowledge of the frequent association of hypertension with chronic interstitial nephritis and arteriosclerosis, to associate both the renal and arterial disturbances with some alteration of the adrenal. These suggestive facts, taken in connection with the rapidly accumulating evidence of intimate chemical correlation between widely separated organs, renders the problem an exceedingly interesting and suggestive one.

Within the past three years French investigators, led by Vaquez, have contributed a large mass of literature which indicates that localized or diffuse hyperplasia of the adrenal is commonly associated, when the disease does not run too rapid a course, with contracted kidney and arteriosclerosis. The hyperplasia is considered as an indication of hyperactivity of the antitoxic and angiotonic functions of the gland, what we might call perhaps hyperadrenalism.

The literature of this subject is now so voluminous that it would be unwise to review it completely, especially as the anatomical studies have been recently very completely collected and described by Rose,[3] and the somewhat scanty and not very convincing experimental studies have been similarly treated by Darré.[4] To indicate, however, the observations upon which this theory is based a portion of the earlier literature should be given briefly:

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[1] Work aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Exper. Med.*, 1908, x, 735.

[2] Pearce, R. M., The Theory of Chemical Correlation as Applied to the Pathology of the Kidney. Annual address before the Philadelphia Pathological Society, April 23, 1908.

The first case described by Vaquez was one of adenoma of the cortex of the adrenal associated with a contracted kidney. Josué described three instances of diffuse arteriosclerosis with hypertrophy of the adrenal. Aubertin and Ambard studied eight cases in which there was contracted kidney and found fatty adenoma in three, diffuse hyperplasia in four and in the remaining case with a rapid clinical course a normal adrenal. Lemaire in a single instance, and Froin and Rivet in six out of seven cases of nephritis found adenomata or nodular hyperplasia; the remaining patient, in whom the rise in blood pressure was slight, had a normal adrenal. Menetrier found two adenomata in seven patients with contracted kidney. These figures indicate the frequency with which pathological changes have been described in the adrenals in association with renal and vascular lesions. There are many negative findings however and the frequency of similar lesions with diseases other than those of the kidney and vascular system have not been sufficiently investigated. On the other hand Landau[5] who has examined the adrenals of sixteen individuals, suffering from general arteriosclerosis between the ages of forty-nine and ninety-six years found no changes which might not be ascribed to the effect on the gland of arteriosclerosis of the vessels of the adrenal itself.

In the hope of throwing more light on the subject by purely anatomical studies I have examined the autopsy records of the Bender Laboratory and have attempted to determine the relation of vascular and nephritic lesions to changes in the adrenal. Attention has been paid also to the occurrence of hyperplasia of the adrenal in association with conditions other than chronic vascular or renal disease.

It has not been an easy matter in all instances, on account of the slighter variations so common in the adrenal, to establish a dividing line between a "normal picture" and the changes in the gland considered by the French writers to be characteristic of chronic interstitial nephritis. An arbitrary normal standard was finally established by comparing the descriptions of several histologists with sections of the adrenal of twelve individuals between the ages of forty and fifty-six years who had met death by violence and were free from chronic disease of any kind, and whose glands were therefore presumably normal for the ages given. The validity of the establishment of this normal picture was further strengthened by the study of glands of forty-six individuals under thirty years of age dying as the result of various acute infectious diseases. In this way the more acute degenerative changes were controlled.

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[3] Rose, F., Blutdrucksteigerung, Schrumpfniere und Nebennieren, *Med. Klinik*, 1907, iii, 1405.

[4] Darré, H., De l'influence des altérations du rein sur les glandes surrénales, Paris, 1907.

[5] Landau, H., Ueber die anatomischen Veränderungen in den Nebennieren bei Arteriosklerose, *Zeitschr. f. klin. Med.*, 1907, lxiv, 227.

On the other hand the descriptions of Aubertin and Ambard[6] and of Vaquez and Aubertin[7] have been taken as depicting accurately the changes deemed by the French writers to be characteristic of chronic interstitial nephritis with hypertension. Their histological descriptions may be summarized as follows: The earliest lesion is a "non-fatty" nodule of the glomerular zone involving to some extent the fascicular zone. This change may be found in other conditions, but is more marked in chronic interstitial nephritis. Another early appearance is a "fatty" nodule well limited and isolated in the midst of normal cells and seen especially in the fascicular zone. The latter may sometimes be very numerous and not sharply limited. The final stage is a *hyperplasia adenomatosa totale* with definite increase in the weight of the gland. A true macroscopic adenoma of the adrenal they state to be of no significance, unless associated with diffuse hyperplasia. It differs from the so-called adenoma of nephritis in that the latter is a more marked or accentuated local manifestation of a diffuse process, while the ordinary macroscopic adenoma develops in an otherwise normal gland.

It must be here stated that these writers have never limited these lesions to the adrenal of chronic interstitial nephritis but have said, that if individuals of very advanced age are eliminated, the lesions are found in nineteen of twenty cases of the interstitial type of nephritis and but once in twenty cases of the parenchymatous type, or in other diseases than interstitial nephritis. They do insist, however, that these lesions are always accompanied by hypertension except in those cases of chronic nephritis running a very rapid course.

The material of the present study consists of 163 adrenals which have been divided into groups according to the ages of the individual and the presence or absence of chronic renal and vascular lesions. They were selected from a group of 1,200 autopsies and include all sections of the adrenal which pass through the center of the entire gland and are well preserved and well stained. They are therefore representative of the lesions occurring in the average run of autopsy material. In no case, however, have we notes of the blood pressure during life. For this reason the study of material of this kind is not comparable, strictly speaking, to the studies of the French investigators as the latter, for the most part, used only material from individuals who during life showed definite hypertension. The purely anatomical studies here presented are, however, of value as control observations and form a basis for a detailed study, now in progress, of the adrenal from individuals exhibiting hypertension clinically.

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[6] Aubertin, C., and Ambard, L., Lésions des capsules surrénales dans les néphrites avec hypertension, *Bull. et mem. d. l. soc. med. h. hôp. d. Paris*, 1904, xxi, 175.

[7] Vaquez and Aubertin, C., Sur l'hyperplasie surrénale des néphrites hypertensives, *ibid.*, 1905, xxii, 705.

Group I. Normal Glands.—This group includes twelve glands from individuals between forty and fifty years of age (average forty-four years) who met sudden death from some form of violence. They are taken as normal controls.

Group II. Glands from Individuals under Thirty Years of Age Dying of Infectious Diseases.—This group includes forty-seven glands of which fourteen are from infants and sixteen from children. They were taken as controls of the acute degenerative or other lesions which might be caused by infection. The diseases represented are diphtheria, typhoid fever, tuberculosis and noma, acute infections of the respiratory system, and diseases of the gastro-intestinal tract, middle ear, and uterus. In only eight examples could departures from the normal structure be found. These occurred in three glands of general tuberculosis, in two of typhoid fever, and one gland each of diphtheria, pelvic abscess and septic endometritis. All were in individuals over twenty years of age. In one gland of the tuberculosis group, a diffuse hyperplasia of the fascicular zone with the characteristic spongy appearance, and in another a very definite nodular hyperplasia of the glomerular zone occurred; in two excessive pigmentation and in all a hyperplasia of the medulla existed. In one also a slight diffuse increase of connective tissue was present and in another some round cell infiltration. In the case of acute septic endometritis a very definite hyperplasia of the medulla with round cell infiltration existed. In one gland from a case of typhoid fever were noted focal necroses with extensive leucocytic infiltration and in the other multiple nodular hyperplasia of the glomerular and fascicular zones and diffuse hyperplasia of the medulla. In the glands from cases of diphtheria and pelvic abscess nodular adenomata were also present with more or less diffuse " fatty " changes. In connection with the changes in the adrenals of tuberculosis individuals here described it is noteworthy that Aubertin and Clunet[8] have described hyperplasia of the medulla in five cases of tuberculosis.

Group III. Glands from Individuals Over Thirty Years of Age, Free of Chronic Vascular and Renal Disease.—This group includes nineteen glands from individuals between thirty-one and fifty-seven years of age (average forty-four years). They are to be regarded as controls for the glands derived from individuals of the arteriosclerotic period. Eight showed no adenomatous changes, while in eleven were found the changes described by Vaquez and Aubertin. The hyperplasia was nodular in eight, diffuse in three and combined in two; in three of the nodular variety the lesion was of the " fatty " type. Increase of connective tissue was found in three glands from cases of syphilis, tuberculosis and cancer, respectively, with, in the first, considerable round cell infiltration. Excessive pigmentation was present in two glands of chronic mitral endocarditis. Hyperplasia of the medulla occurred in two instances in association with syphilis and chronic mitral disease, an association which has also been noted by Aubertin and Clunet.

Group IV. Glands from Individuals Over Thirty Years of Age, with Contracted Kidney, Arteriosclerosis and Heart Hypertrophy.—This group has been very carefully selected and comprises twenty-four glands from individuals who suffered from typical chronic nephritis of the interstitial type (contracted kidney) associated with well-marked general arteriosclerosis, involving the aorta or its larger branches, and with hypertrophy of the left ventricle (in four instances both ventricles) of the heart. That is, it represents the anatomical material corresponding to the typical clinical features of chronic vascular and renal disease with which hypertension is usually associated. The ages varied from thirty-eight to eighty-seven years (average, fifty-nine years).

Only one of these glands could be considered absolutely normal. Sixteen showed changes which must be considered as the result of the effect on the gland of the arteriosclerotic changes in its own vessels. These changes are similar to those found in the kidney, pancreas and other organs when their vessels are altered by arteriosclerosis. The vessels of the medulla and capsule show fibrous and hyaline thickening with diminution of lumen, the capsule is thickened and both cortex and medulla show various grades of connective tissue increase and round cell infiltration.

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[8] Aubertin, C., et Clunet, J., Hypertrophie cardiaque et hyperplaise médullaire des surrénales, *C. r. Soc. de Biol.*, 1907, lxiii, 595.

In all instances, in addition to these productive changes, certain lesions described by the French writers were present to some degree, and most frequently the diffuse hyperplasia combined with simple nodules of either the "fatty" or "non-fatty" type.

Similar hyperplastic lesions were found in the seven glands in which evident fibrous and local vascular changes were absent, though in three of them, it should be noted, round cell infiltration was a prominent condition.

In six glands of this group a definite hyperplasia of the medulla was apparent, and in two pigmentation was very marked; in almost all the glands it was greater than normal.

The relation of the adenomatous changes to the local lesions due to arteriosclerosis, in the sixteen glands first described, might be explained as compensatory to gland injury and analogous to the "multiple nodular hyperplasia" seen in the liver in cirrhosis and in repair of acute yellow atrophy or after other destructive lesions. This explanation cannot on the other hand be applied to the simple hyperplasia observed in the seven glands without connective tissue proliferation. The hyperplasia, however, is no more frequent in these glands than in Groups II and III in which chronic vascular and renal lesions do not come into question.

Group V. Arteriosclerosis Associated with Chronic Nephritis of the Parenchymatous Type.—This group includes thirteen glands from individuals who showed arteriosclerosis of the same grade as the previous group, but in whom chronic parenchymatous nephritis instead of the interstitial type existed. This material was very carefully selected in order to exclude the latter and to include examples of general vascular lesions of the same degree as in the latter disease. The ages varied from thirty-eight to eighty years (average, fifty-seven years).

Of these glands two were normal, five showed vascular and connective tissue lesions of the character seen in Group IV, associated in three with hyperplasia, and six showed hyperplasia only.

The conditions therefore are not essentially different from those of the previous group and do not support the view of the greater importance of chronic interstitial nephritis as productive of hyperplasia of the adrenal.

Group VI. Arteriosclerosis without Chronic Nephritis.—This group comprises sixteen glands obtained from individuals with well-marked arteriosclerosis of the aorta and larger vessels but without chronic nephritis of any type. The fatalities include various infections and the chronic diseases common to the latter half of life. The ages vary from thirty-five to seventy-four years (average, fifty years).

Of the sixteen glands, ten showed the vascular and connective tissue changes previously described as characteristic of the arteriosclerotic gland. In all but three of these, adenomatous lesions also exist. Four exhibited hyperplasia only, and two were normal.

These observations compared with those made of Groups IV and V indicate that the constant factor in producing the hyperplasia is arteriosclerosis; and hyperplasia occurs indifferently in chronic nephritis of the parenchymatous type, of the interstitial type, and in absence of chronic nephritis of all types.

Group VII. Chronic Nephritis without Arteriosclerosis.—This group includes twelve glands obtained from individuals without arteriosclerosis but who had definite chronic nephritis, which in ten was of the parenchymatous and in two of the interstitial type. Incidentally this group bears on the question of the frequency with which chronic interstitial nephritis occurs in the absence of arteriosclerosis. The ages ranged from twenty-three to fifty years (average, thirty-six years).

Five of the glands were normal. Two, from individuals with pneumonia and gangrene of the leg, respectively, showed diffuse hyperplasia with discrete non-fatty nodules; and four showed nodular adenomata only. The remaining gland from an individual with tertiary syphilis presented very extensive round cell infiltration of the medulla, but no hyperplasia. Extensive round cell infiltration was present also in the gland from an individual with gangrene of the leg; and slight infiltration in one of chronic mitral disease. In no instance was an increase of connective tissue present. Of the two cases of interstitial nephritis one gland showed nodular hyperplasia and the other none.

These findings are in accord with those previously presented as far as the influence of chronic nephritis of the interstitial type is concerned and indicate, as do the findings in Groups II and III, the relative frequency of hyperplasia of the adrenal in the absence of arteriosclerosis.

Group VIII. Does Hyperplasia Occur in Chronic Destructive Lesions of the Adrenal?—In another section (Group IV) the statement has been made that the adenomatous hyperplasia of the adrenal, in chronic productive lesions of the gland, might be in part a compensatory process analogous to the nodular hyperplasia occurring in the liver of cirrhosis. An attempt has been made to determine whether such a hyperplasia occurs in the persisting tissue of adrenals which are the seat of extensive chronic destructive processes. Two glands invaded by carcinoma, two with amyloid and ten with tuberculosis have been studied. In two of these, cancer and amyloid respectively, a nodular hyperplasia of the "non-fatty" type was demonstrable in the glomerular and fascicular zones, while in four of the tuberculous organs areas were found which could be interpreted only as the result of hyperplasia. These masses do not show the normal architecture of the adrenal, but are atypical and consist of very large pale vacuolated cells usually containing considerable pigment. The masses are located, frequently, at a distance from the tuberculous lesions and encased in connective tissue. In one gland in which considerable portions of the organ remained intact a diffuse hyperplasia was present.

These findings support the theory of a compensatory nodular hyperplasia of the adrenal, and suggest a possible explanation of the relatively constant hyperplasia of the arteriosclerotic gland.

Group IX. Macroscopic Adenoma of the Adrenal and Kidney (Hypernephroma).—Although Vaquez and Aubertin state that macroscopic adenomata are of no importance in the production of hypertension or in the relation of the adrenal to chronic nephritis, I have grouped these cases in order to present the subject in complete form.

Three hypernephromata of the kidney and three adenomata of the adrenal were available for study. One of the latter was from an individual of thirty-eight years of age who was free from renal and cardio-vascular lesions. The other five were all from individuals between fifty and sixty years of age. Chronic nephritis of the parenchymatous type was present in two and of the interstitial type in two individuals; and the kidney was normal in one individual. In three of the cases a well-marked general arteriosclerosis and in two slight lesions of the aorta and coronary arteries existed. Heart hypertrophy was absent in all.

Macroscopic adrenal adenomata would therefore appear to have no definite relation to chronic interstitial nephritis; whether they bear any relation to arteriosclerosis cannot be concluded from the small number of examples in my studies.

SUMMARY.

Vaquez and Aubertin advance three theories in explanation of the adrenal hyperplasia; first, that it may not be the cause of hypertension but "an antitoxic hyperplasia" caused by the retained products of metabolism which may be responsible also for the hypertension; second, that it may be the cause of hypertension but secondary to the renal lesion; third, that it may be the cause of hypertension but may antedate the renal lesion or be entirely independent of it. They, as well as other French writers, insist that this hyperplasia is almost constantly associated with chronic nephritis of the interstitial type and it is seldom found with the parenchymatous type of nephritis, or with other lesions.

Hyperplasia of the adrenal, as far as my material enables one to judge, does not occur during the first and second decades. In the third decade it is relatively frequent in the absence of chronic arterial and renal disease but reaches the maximum in association with such disease after the fourth decade. It is an almost constant lesion in arteriosclerosis associated with chronic interstitial nephritis and left-sided heart hypertrophy, but occurs with almost equal frequency in arteriosclerosis with chronic nephritis of the parenchymatous type. It is a relatively frequent lesion of arteriosclerosis without chronic nephritis and of the latter without arteriosclerosis also. As the result of this analysis one is lead to the view that while hyperplasia of the adrenal is a very frequent concomitant of chronic renal and arterial disease it is not exclusively a feature of either type of nephritis or yet of chronic vascular disease; but it probably represents the effect of some factor operating in that period of life in which chronic renal and arterial affections are most frequent.

Worthy of special emphasis is the observation that the characteristic lesion of an adrenal, the seat of local arteriosclerosis, is of the type of the chronic productive inflammation seen in arteriosclerosis of the pancreas and kidney; that is, thickening of the vessels, increase of connective tissue and round cell infiltration. Associated with these changes is a hyperplasia which is very constant, and which may be, in part, of the nature of a compensatory hyperplasia similar to that seen in the liver of cirrhosis and acute yellow atrophy. A hyperplasia of this type, as has been shown, may occur in destructive lesions of the gland. This, however, does not explain hyperplasia in the absence of local vascular changes which fact is, possibly, as suggested by Landau, evidence, not of a correlation between kidney and adrenal, but of a vicarious hypertrophy depending upon lesions of some other organ of the body than the kidney, possibly some other ductless gland, affected by arteriosclerosis or other disease.

CLINICAL NOTES AND PHYSICOCHEMICAL STUDY OF SALT ELIMINATION IN THE URINE OF AN INDIVIDUAL WITH GENERAL EDEMA OF OBSCURE ORIGIN, FOLLOWED BY CURE.*

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This case of general edema of obscure origin without evidence of kidney lesion is reported in part on account of its interest clinically and in part because of the unusual importance of the results of the physical and chemical examination of urine. Incidentally, therapeutic observations difficult of interpretation but apparently of some value are also presented.

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* This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association, and is from the Bender Laboratory, Albany, N. Y.

Clinical Report (A. W. Elting).

Patient. G. H. R., aged 45, an experimental chemist by occupation, was first seen in July, 1907, at which time he complained of irritation of the throat, general debility, and inability to concentrate his attention on his work.

History. His family and past history were negative, except that for the last ten years most of his time had been spent in a much vitiated atmosphere due to the decomposition at high temperatures of linseed oil, gums, resins and hydrocarbon compounds. These vapors are for the most part acid, readily form metallic salts, and are as a rule irritating to the urinary tract. The patient used alcohol and tobacco moderately and gave an indefinite and improbable history of chancre twenty years ago, with no subsequent luetic manifestations.

Onset of disease. He had noticed for several years past that when subjected to the fumes above described he would be troubled by irritation of the urinary tract and of the throat. During the winter of 1903 he first observed an occasional swelling of the palmar surface of the fingers, and about the same time some slight enlargement of the upper part of the abdomen. He also became fatigued on slight exertion and very languid. Moderate doses of blue mass relieved these conditions temporarily. In 1905 the feeling of lassitude became quite constant. He would arise in the morning feeling fairly well, but on moving about would soon become tired. He was also troubled with drowsiness during the day, sometimes falling asleep at his desk. Nervousness was an almost constant symptom, for which no definite cause could be assigned, and he suffered from slight lapses of memory and was at times much troubled with a cough. On retiring at night he would fall asleep for a short time and then awaken with a nervous start which would be followed by insomnia for the rest of the night. In April, 1907, he noticed some puffiness about the lower eyelids, which later extended to the temporal region. About this time he found that he could not lie with his head low in bed without experiencing a sensation in the ears similar to that caused by water. When the patient was seen in July there was very slight puffiness about the lower eyelids and face, with moderate chronic laryngitis, but no other evidence of physical disorder. The usual urine examination at that time was negative. In August and September the edema increased somewhat in the face and extended to the neck, chest, upper part of the back and the upper extremities. He was seen again about October 1, 1907, at which time the edema in the above-mentioned localities was quite pronounced and there was slight dyspnea and cyanosis. A suspicion of mediastinal tumor was entertained, but absolutely no physical evidence of such a condition could be detected. The urine examination was negative (chlorid elimination was not tested). The patient was advised to give up his work for a time and go to his home in Pennsylvania. This he did. About this time the cough became much aggravated and more paroxysmal in character, accompanied by vertigo and semi-unconsciousness for a few seconds. The patient also found it impossible to lie flat in bed because of dyspnea and was compelled to sleep propped up.

About October 15, 1907, the attacks of coughing became much more severe and breathing more labored; the expectoration was slight in amount and consisted of a frothy mucus. The edema gradually extended downward over the trunk, then involved the scrotum and finally, but gradually, the legs. The patient's condition became desperate because of the attacks of coughing, the dyspnea and the cyanosis, and with much difficulty he was brought from his home in Pennsylvania to St. Peter's Hospital, where he was admitted October 30, 1907.

Condition on Admission. This was alarming. Dyspnea was very marked and increased on the slightest exertion. Cyanosis was pronounced and there was a most extensive edema of the face, neck, chest, back and upper extremities, less marked over the lower part of the trunk, the scrotum and lower extremities. The patient suffered from frequent paroxysms of coughing, and at these times he would have mild convulsive seizures and become unconscious for a few seconds. It was impossible for the patient to lie down and he sat propped up in a chair. The edema was of a firm character and seemed to involve the muscles and deeper tissues rather than the subcutaneous tissues.

Physical Examination. There was absolutely no evidence of any accumulation of fluid in the serous cavities. Examination of the heart and lungs was negative except for sibilant, sonorous and some small moist râles. The abdominal viscera were normal. The temperature was subnormal and the pulse about 100. The quantity of urine was much reduced, varying from 300 to 500 cubic centimeters in twenty-four hours. The patient was extremely nervous and slept but little. His appetite was poor. The blood examination was negative. Satisfactory radiographs of the thorax were obtained, but these were normal and there was no evidence whatever of mediastinal tumor or aneurism. Nervousness was a constant and pronounced symptom, as was insomnia. The patient's condition for the first week after admission to the hospital was most desperate, chiefly because of the attacks of dyspnea and coughing, during which he would frequently lose consciousness. The appetite was very poor.

Treatment. On admission to the hospital the patient was given large quantities of liquids and iodid of potash in increasing doses.

November 10: The administration of acetate of potash and infusion of digitalis apparently caused some increase in the volume of urine.

November 12: A steam bath was given without any evident increase in the perspiration, the patient's skin having been unusually dry at all times and perspiration evidently very much below the normal. Heroin in one-twelfth grain doses seemed to be quite effectual in relieving the cough. He was unable to lie down and spent all his time propped up in a chair.

November 21: He suffered a very severe attack of dyspnea and became unconscious. Oxygen, amyl nitrite and nitroglycerin were freely used and resuscitated him. The patient was given an ounce of magnesium sulphate every other morning and the stools were quite watery in consequence.

November 25: He was placed on as nearly a salt-free diet as could be secured, and from this date until February 1, 1908, a somewhat complete quantitative examination of the urine was performed daily, the results of which follow the clinical report.

November 27: The diuretic mixture was discontinued.

December 8: The patient was given potassium nitrate in fifteen grain doses every three hours. As the result of the administration of this the volume of the urine increased until on December 12 it amounted to 3,225 cubic centimeters (Table 2). Coincident with this there was a marked diminution in the edema and a decided improvement in the general condition. Attempts were also made to give the patient subcutaneous infusions of sterile water, but these had to be abandoned because of the great pain they occasioned. He was, however, given twelve ounces of sterile water by rectum each day. The potassium nitrate was discontinued on December 12 and was resumed on December 14, with but little effect on the volume of the urine, but the chlorid output was markedly increased.

December 13: The patient was given an artificial Nauheim bath and this was repeated on two successive days with apparently a marked softening and lessening of the edema and a decided improvement in the cough and dyspnea.

December 27: Another series of artificial Nauheim baths was given on alternate days with a lessening of the edema. About this time the patient was able to assume a somewhat reclining posture at night and gradually as his condition improved his position in sleeping approached more and more the horizontal. About January 1, 1908, the patient began to take a few steps, but was easily exhausted and was very weak.

January 4: He experienced a very severe attack of coughing and dyspnea and the edema increased slightly.

January 20: A small fixed quantity of salt, 5 grams per diem, was added to the food, but the patient objected strongly, stating that it nauseated him. Gradually, however, he became accustomed to it and the dislike for salt disappeared.

Clinical Course. The course of the edema was variable; as a rule, when the urine increased the edema decreased. The edema first disappeared from the chest, then the face and the back, the legs and forearms being the last to yield. Gradually the patient was encouraged to take more exercise and to get out of doors for a short time each day. This seemed to exert a very beneficial effect on the edema, and the dyspnea and coughing seemed to vary with the edema.

Later Course. The patient left the hospital on February 1, 1908. At this time there was still some edema in the forearms and legs, and some dyspnea, which increased on exertion. His general condition was fairly good. His strength was greatly improved and he was voiding about a normal amount of urine. He was then able to sleep in the horizontal position and was decidedly less nervous. The week following discharge from the hospital was spent at his home. The urine varied from 600 to 900 cubic centimeters in twenty-four hours, and the patient's appetite was somewhat improved. At the end of one week he started for Bermuda. The sea air increased the cough and expectoration somewhat, but the breathing was less labored. Shortly after arriving in Bermuda he was taken with a chill, followed by a fever which lasted for a day or two. He had great thirst and drank large quantities of water. At this time he had massage each day for three or four days and the urine rapidly increased to 3,000 cubic centimeters in twenty-four hours. He was on a light diet with large quantities of fruit, especially oranges. From Bermuda he went to Nassau, where the temperature was higher and where he was able to take more exercise and felt much better. The urine ranged from 1,500 to 1,800 cubic centimeters daily. Early in March the patient returned to Pennsylvania, much improved in every way, the edema less marked, his strength greatly improved and with but little dyspnea on exertion. When the patient was seen June 10, 1908, there was but slight edema, traces being found in the neck, forearms, calves and about the ankles; this, as previously, seemed to be muscular rather than subcutaneous. The edema appeared to be more or less transitory. Sleeping in the sitting posture increased the edema of the legs, while sleeping in the recumbent posture increased it in the face, neck and arms. Exercise rapidly lessened the edema. The general health was good and the appetite was normal. Since the middle of February the patient has taken no medicine, except one ounce of Rochelle salts every other day and an occasional eight-grain blue mass pill. The cough has entirely ceased, except on severe exertion, and when it does occur it is without the previous spasmodic character. The patient has resumed part of his duties.

EXAMINATION OF THE URINE (H. C. JACKSON).

As stated in the clinical notes, a preliminary examination of a twenty-four-hour specimen of the urine of November 21, 1907, showed a small volume of 340 cubic centimeters with a normal specific gravity of 1025. Qualitative tests indicated that no pathologic substances were present. The first indication of an abnormality was shown on testing for chlorids by the addition of silver nitrate to the urine made acid with nitric acid. The slightest precipitate, amountng to only an opalescence, resulted, indicating a practical absence of chlorids. At this time the patient was living on an ordinary hospital diet. Orders were immediately given for the preparation of a special diet which was as nearly free from salts, especially sodium chlorid, as could be obtained. Fluids were given in as large quantities as possible. The regular examination and analysis of twenty-four-hour samples of urine began on November 24, 1907, and continued until February 1, 1908, in all ten weeks. The analysis consisted in the determination of the volume, specific gravity, total nitrogen according to Kjeldahl's method, chlorids by Volhard's indirect method, phosphates by titration with uranium nitrate and the depression of the freezing point Δ by means of the ordinary Beckmann apparatus. At various times during the period of observation the ammonia and uric acid were estimated and were found to be normal in amount and in percentage of total nitrogen. At no time could albumin or casts be detected. The whole time of observation has been divided into four periods of from ten to thirteen days each. The first represents the time during the change from the normal to salt-free diet and includes nine days on the latter diet. The second follows the first, after a lapse of three days, and consists of the days just before, during and after the administration of potassium nitrate during a salt-free diet. The third, with three days' interval, represents the effect of the artificial Nauheim baths on the patient, who was still on the same diet. The fourth and last period begins after a lapse of eleven days, during which time the condition of the patient was steadily improving on the salt-free diet and continues during the period when an approximately normal diet was resumed. The patient, during the period of forced restraint from salt, developed a decided dislike to the condiment and it was only with considerable difficulty, by persuasion and by placing the salt in the food during preparation, that he was induced to take a definite amount (five grams) each day during the final period of normal diet. The tables for the four periods follow, with the discussion of the important points brought out in each:

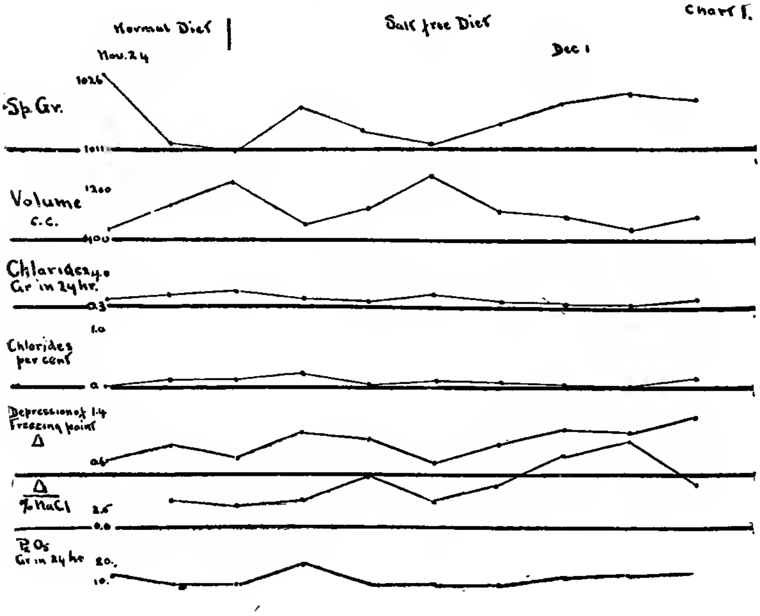
Period I.

Previous to November 24, 1907, the daily volume of the urine averaged from 150 to 300 cubic centimeters and the administration of digitalis and potassium acetate and digitalin had little effect as regards the volume of output. It will be seen in the clinical report that the administration of water on the salt-free diet benefited this condition somewhat, as the volume rose at times to almost the normal with the specific gravity only a little below the average. The absolute chlorid elimination averaged almost two grams on the normal diet. This amount fell gradually during the salt privation, although at times it reached nearly to the normal diet figures for this individual. It is interesting to note that the chlorid percentage output did not vary with the absolute output of chlorin or with the elimination of water, but with some few exceptional days remained between 0.16 and 0.32 per cent. (see also the first two days in Table 2). This fact seemed to indicate that during the period of hydremic plethora following the ingestion of larger quantities of water the blood was able quickly to resume its then normal osmotic concentration by drawing from the salt of the tissues, and that the filtrate passing through the glomerulus was constant in composition and was normally concentrated in the convoluted tubules. On the other hand, the depression of the freezing point runs parallel with the specific gravity and inversely as the volume and in no relation to the chlorid output, absolute or percentage. Evidently, then, the nitrogenous constituents (urea, uric acid, kreatinin, etc.) were being eliminated in normal manner and variations in their output and percentage relations were causing the ordinary changes in specific gravity and depression of the freezing point. Neglecting the abnormally low chlorid elimination, and hence low specific gravity in relation to the volume of urine excreted, the other physical factors reacted perfectly normally. Thus no evidence could be obtained in any way, at any stage of the investigation, that the renal function was affected in the slightest degree. The phosphoric acid elimination was somewhat below the average, but,

TABLE 1.

Date	Vol. cc.	Sp. Gr. 1.0—	Chlorids Grams	Chlorids Per Cent.	P_2O_5 Grams	Δ	$\frac{\Delta}{\text{NaCl}}$	
11/24	415	27	1.34	0.32	1.42	....	....	Normal diet.
11/25	800	13	1.92	0.21	1.07	0.87	4.1	Normal diet.
11/26	1150	11	2.53	0.22	1.10	0.665	3.2	Salt-free diet.
11/27	515	20	1.43	0.27	1.81	1.085	4.0	Salt-free diet.
11/28	700	15	0.84	0.12	1.14	0.950	7.9	Salt-free diet.
11/29	1220	12	1.95	0.16	1.16	0.545	3.4	Salt-free diet.
11/30	650	16	0.91	0.14	1.21	0.865	6.1	Salt-free diet.
12/1	535	20	0.53	0.10	1.47	1.100	11.0	Salt-free diet.
12/2	...	..	....	....	....	.....	....	
12/3	365	22	0.29	0.08	0.66	1.090	13.6	Salt-free diet.
12/4	540	21	1.08	0.20	1.49	1.280	6.4	Salt-free diet.

CHART OF TABLE 1.



when considered in connection with the diet and amount of nitrogen excreted, it was considerably above the normal. We believe that the high $\frac{\Delta}{\mathrm{NaCl}}$ factor was without value as an indication of any disturbed circulatory, cardiac or renal lesion (Korányi[1]), since this factor paralleled almost exactly the concentration of the urine as indicated by the specific gravity and depression of the freezing point.

Period II.

On December 9, 1907, the administration of potassium nitrate in doses of fifteen grains every three hours was begun and continued for three days followed after one day's intermission by a second period of three days with similar treatment. During all this time the salt privation was continued. The nitrate was selected[2] since, according to Sollmann, sodium nitrate stands as one of the few diuretics which occasions an increased percentage output of sodium chlorid coincident to the diuresis. The explanation offered by Sollmann is that the nitrate replaces the sodium chlorid in the tissues, thus throwing the latter substance out of combination and allowing of its excretion. In view of the relatively small amounts of potassium nitrate administered and the tremendous elimination of sodium chlorid which it caused, such an explanation seems hardly probable or even possible. As the table indicates, the potassium nitrate during the first period of ingestion caused a diuresis during which the volume increased to 3,225 cubic centimeters on the last day; the specific gravity was not markedly lowered owing to the fact that the percentage output of sodium chlorid was doubled; on the last day the absolute excretion of chlorids reached seventeen and four-tenths grams. The Δ remained unchanged; the increased concentration of the chlorids being counterbalanced by the decreased percentage elimination of the other soluble constituents of the urine, as is normally the case during diuresis. This again supports the view that the increased percentage output of chlorids is due to an increased ionic concentration of the blood in terms of this ion. The factor $\frac{\Delta}{\mathrm{NaCl}}$ was reduced to the normal figures during this and the subsequent potassium nitrate period. The phosphoric acid output was somewhat increased in absolute amount, but the percentage figures were lowered during the diuresis. The second period of potassium nitrate ingestion differed slightly from the former in that the diuresis was not very evident; the increased chlorid output was quite pronounced, although not so marked as in the first period. This condition caused the Δ to increase and percentage of chlorid elimination to rise on one day

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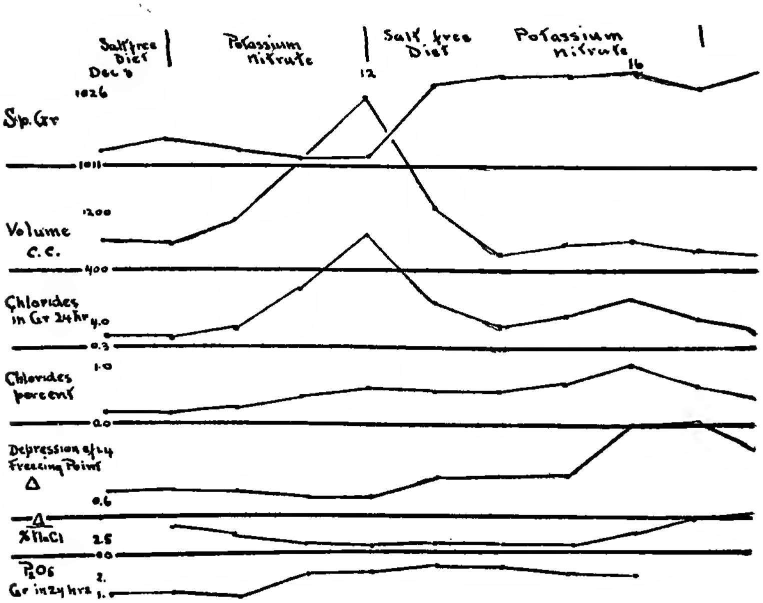
[1] v. Korányi, A.: Physiologische und klinische Untersuchungen uber den osmotischen Druck thierischen Flüssigkeiten. *Ztschr. f. klin. Med.*, 1897, xxxiii, i; 1898, xxxiv, i.

[2] This substance was employed following the work of Sollmann (The Effect of Diuretics, Nephritic Poisons and Other Agencies on the Chlorids of the Urine, *Am. Jour. Physiol.*, 1903, ix, 423), who showed the diuretic effect of sodium nitrate and its power to increase both the absolute and percentage elimination of chlorids. The potassium salt was chosen in the hope that the well-known effect of these salts in replacing sodium compounds in the body (Bunge) might aid in producing a favorable result.

TABLE 2.

Date	Vol. cc.	Sp. Gr. 1.0—	Chlorids		P₂O₅ Grams	Δ	Δ / NaCl	
			Grams	Per Cent.				
12/8	850	14	2.04	0.24	1.51	....	....	Salt-free diet.
12/9	785	16	1.41	0.18	1.48	0.800	4.4	Salt-free diet.
12/10	1140	14	2.74	0.24	1.28	0.740	3.08	Pot. nitrate.
12/11	2110	12	8.86	0.42	2.00	0.650	1.50	Pot. nitrate.
12/12	3225	12	17.40	0.54	2.13	0.660	1.22	Pot. nitrate.
12/13	1300	26	6.50	0.50	2.08	0.775	1.55	Salt-free diet.
12/14	580	30	2.72	0.47	2.24	.....	....	Pot. nitrate.
12/15	700	28	4.06	0.58	3.42	0.875	1.50	Pot. nitrate.
12/16	790	30	6.95	0.88	2.27	1.765	2.00	Pot. nitrate.
12/17	610	24	3.42	0.56	1.98	1.845	3.33	Salt-free diet.
12/18	525	28	2.10	0.40	....	1.335	5.45	Salt-free diet.
12/19	615	20	1.48	0.24	....	1.470	6.12	Salt-free diet.

CHART OF TABLE 2.



to almost normal figures. During the six days of drug administration and the two single days following each period, fifty-two and sixty-five hundredths grams of sodium chlorid were excreted, and this during a salt-free diet.

If we consider the weight of the patient at seventy-five kilos and deduct therefrom the proportional fraction of this due to bone, by a simple calculation one can determine that the presence of these fifty-two and six-tenths grams of sodium chlorid in the body before its elimination would have been sufficient to increase the osmotic concentration of the fluids of the whole body equivalent to that of about a one per cent. sodium chlorid solution. This will serve to indicate the extreme state of hypertonicity which must have existed in the fluids of the body before the administration of the potassium nitrate and to which it is believed the edema was due.

This period of somewhat incomplete analytical results covers the time of gradual recovery with continued salt privation. During part of this time, beginning on December 27, 1907, the patient was given a series of artificial Nauheim baths on alternate days, with the intention of stimulating the peripheral circulation. All previous attempts to cause sweating by hot baths, etc., had been fruitless. While the results are hard to explain, they are too evident to admit of doubt as to cause and effect. No change in the volume of urine was noticed, but the increased elimination of chlorids brought the percentage output almost up to normal on December 30 and to one and seven-tenths per cent. on December 28. During the period between January 1 and 12 the effect of abstinence from sodium chlorid became evident in the extreme lowness of the absolute output, amounting on the average to only forty-five one hundredths gram. This can be seen on examination of the first three days, Table 4.

Period IV.

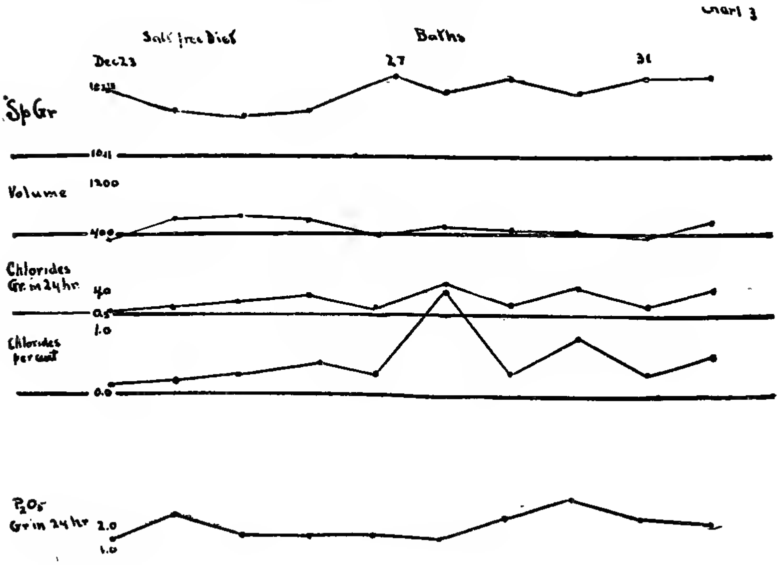
This table details the results of the commencement and continuance of a somewhat normal diet in which sodium chlorid was not excluded, but during part of which sodium chlorid was administered in five-gram amounts *per diem.* The first ten days in the table are continuous; then follows a lapse of four days, and a subsequent period of three days is added in order to show the effect of the normal diet two weeks after its commencement. Finally, there follows the results of a partial examination of the urine of the same individual on May 19, 1908, or three and one-half months subsequent to the time when the patient left the hospital (February 1, 1908).

The figures for this period indicate that, while the volume of the urine had not assumed normal figures, the specific gravity was much higher with the same volume than was the case before the treatment began (Table 1). As striking evidence in favor of the view that the edema was set up by chlorid retention, there must be pointed out the tenacity with which the body has retained the chlorids in spite of deprivation of these salts; thus, after about seven weeks of salt-free diet, the body, even at that time, was not in a state of chlorid hunger, since the addition of five grams of salt to the diet caused the elimination, after three days, of over this amount and within the week following the body was almost in exact sodium chlorid equilibrium.

TABLE 3.

Date	Vol. cc.	Sp. Gr. 1.0	Chlorids		P_2O_5 Grams	
			Grams	Per Cent.		
12/23	347	25	0.5	0.14	1.37	Salt-free diet.
12/24	645	20	1.2	0.19	2.16	Salt-free diet.
12/25	705	19	2.1	0.30	1.37	Salt-free diet.
12/26	615	20	3.0	0.48	1.30	Salt-free diet.
12/27	400	27.	1.2	0.30	1.25	Salt-free diet.
12/28	525	21	8.82	1.70	1.00	Salt-free diet + Nauheim bath.
12/29	475	26	1.5	0.31	1.59	Salt-free diet.
1 /30	480	23	4.2	0.88	2.19	Salt-free diet + Nauheim bath.
12/31	390	26	1.4	0.35	1.40	Salt-free diet.
	610	26	3.7	0.60	1.16	Salt-free diet + Nauheim bath.

CHART OF TABLE 3.



That the absolute and percentage output of sodium chlorid have not reached the normal figures is to be attributed to the fact mentioned above, that the patient, on being allowed to resume a normal diet, complained that salt nauseated him and refused to eat foods which tasted at all salty. The Δ and the factor $\frac{\Delta}{NaCl}$ rapidly assumed normal figures after the establishment of the normal diet and have remained so ever since. The phosphoric acid elimination is now well within normal limits.

On the whole, the examination of the urine the day before the patient left the hospital and three and one-half months after shows it to be practically normal when the character of the diet is taken into consideration.

DISCUSSION.

It seems evident that the appearance of the edema noticed in this case was accompanied by a diminished elimination of chlorids; whether this was the result of the edema or its cause is difficult to prove, especially on account of the fact that it was impossible to obtain any of the patient's blood for examination and comparison with the urinary findings. In particular cases of edema associated with certain renal lesions the cause is ordinarily attributed to a deficient eliminating power of the kidney for chlorids. At no time before or during the progress of the disease did any evidence of renal deficiency exist. Apparently, with an increased concentration of the blood for chlorids, there followed an augmented output of these ions. It seems reasonable therefore that the discussion of the renal function in this connection may be excluded.

It is impossible at this time to enter into a complete exposition of the various theories which have been advanced to explain salt retention in relation to hydrops. The subject and its literature have been well covered by Georgopulos[3] and by Christian.[4] The principal contention rests on the question whether the salt retention is the cause or the result of the appearance of the hydrops. Strauss,[5] Widal,[6] Halpern[7] and Castaigne,[8] among others,

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[3] Georgopulos: Experimentelle Beiträge zur Frage Nierenwasserucht, *Ztschr. f. klin Med.*, 1906, lx, 411.

[4] Christian, H. A.: Experimental Nephritis, *Boston Med. and Surg. Jour.*, 1908, clviii, 416, 452.

[5] Strauss: Therap. d. Gegenwart, 1902, iv, 444; 1903, v, 193.

[6] Widal: La cure de déchlorination, *Bull. Méd. des Hôp.*, Paris, 1903, xx, 773, 990.

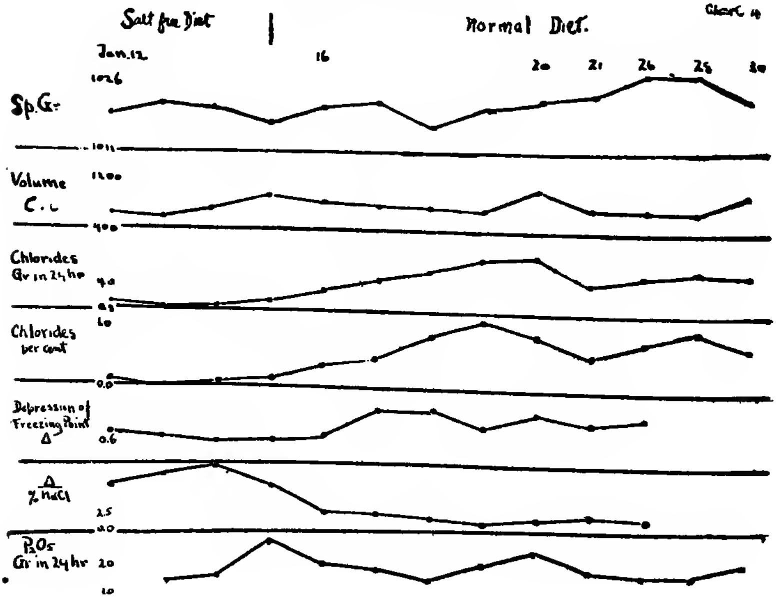
[7] Halpern: Beiträge zur Frage des Verhaltens der Chlorid im Körper, ihre Beziebung zur Oedembildung und ihre Bedeutung fur die Diatetik bei Nephritis. Beitr. z. wissensch. *Med. u. Chem.* (Festschr. f. Salkowski), Berlin, 1904.

[8] Castaigne: Le rôle du reins dans la rétention cholorurée, *Semaine Méd.*, 1903, xxiii, 309; 1905, xxv, 472.

TABLE 4.

Date	Vol. c.c.	Sp. Gr. 1.10–	Chlorids		P_2O_5 Grams	Δ	$\frac{\Delta}{NaCl}$	
			Grams	Per Cent				
1/12	665	18	1.10	0.16	....	1.135	7.08	Salt-free diet.
1/13	605	20	0.38	0.06	1.47	.....	.....	Salt-free diet.
1/14	710	19	0.48	0.09	1.64	0.975	10.80	Salt-free diet.
1/15	935	16	1.30	0.14	2.72	0.990	7.07	Normal diet.
1/16	805	19	2.86	0.35	2.09	1.080	3.08	Normal diet.
1/17	755	20	4.23	0.56	1.86	1.480	2.65	Normal diet.
1/18	715	15	5.58	0.78	1.47	1.450	1.86	Normal diet + 5 grams NaCl.
1/19	675	19	7.31	1.09	....	1.200	1.10	Normal diet + 5 grams NaCl.
1/20	975	22	7.60	0.78	2.42	1.400	1.80	Normal diet + 5 grams NaCl.
1/21	695	23	3.75	0.54	1.79	1.250	2.34	Normal diet + 5 grams NaCl.
....	.....	..	....	....	....	.....	.....	
1/26	665	26	4.67	0.70	1.65	1.345	1.92	Normal diet + 5 grams NaCl.
1/28	660	26	5.54	0.84	1.67	.....	.....	Normal diet + 5 grams NaCl.
1/30	890	21	5.01	0.56	2.22	.....	.....	Normal diet + 5 grams NaCl.
....	...	..	....	....	....	.....	.....	
19/5	1170	15	7.76	0.66	2.45	.....	.....	Normal diet.

CHART OF TABLE 4.



believe that the salt retention in the tissues is primary to the retention of water; the latter observer bases his views on experiments in which saline was injected into normal animals and those with experimental nephritis. The urine in both cases showed no difference. But if sound and diseased animals were bled and saline injected very soon afterwards, the blood of the nephritics contained less salt. The fact that in certain febrile conditions there exists a retention of chlorids without evident renal disturbance is also cited as evidence of the primary nature of the retention. In these cases edema does not necessarily result; and this seems sufficient reason to believe that the factor of permeability of the epithelial lining of the capillaries forms a not unimportant adjunct to the whole process. Müller[9] advances this view and considers that the hydrops is due to an increased permeability of the blood vessels due to certain toxic products in the blood. This conception receives support from Cohnheim and Lichtheim,[10] who showed that subcutaneous edema only followed saline injection when the skin had been irritated in any way, and the results of Magnus with chloroform irritation pointed in the same direction.

In view of the extremely obscure etiology of the case under discussion it would seem to us that a combination of Müller's explanation and that of increased combining power of tissues for chlorids must form the basis for any reasonable explanation of the condition. Nothing in the history of the case points to any anatomic lesion which might account for the hydrops. The appearance in the blood of toxic products inhaled through the lungs as the result of continued sojourn in the vitiated air of a chemical laboratory might readily set up changes in the epithelial lining of the capillaries rendering them more permeable and at the same time bring about changes in the protoplasm of the cell by which the combining power of the proteins would be increased. This in turn would cause an increased osmotic concentration in the cells and as an attempt to reduce this, water would be drawn from the blood. This view would explain, on the one hand, the failure of digitalis and similar agents to cause a diuresis, the dryness of the skin and inability to produce sweating in hot baths; and, on the other hand, the beneficial effects of artificial Nauheim baths in stimulating the cutaneous circulation and capillary epithelium, and the effect of potassium nitrate in starting the replacement of the combined chlorids by means of the nitrate, after which the reduction in ionic concentration, followed by means of mass action. Bunge[11] might be more prone to explain this last process as a replacement of the sodium ion by potassium.

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[9] Müller Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 64.

[10] Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, *Virchow's Arch. f. path. Anat.*, 1877, lxix, 106.

Finally, it must be mentioned that Georgopulos and others present strong arguments against the view that the water retention is secondary to the salt retention. They believe that the kidney becomes more impermeable to water, a hydremic plethora results and the tissues become overladen with water as a result. Georgopulos states with truth that an increase in the salt content of the tissues during the so-called salt retention has never been proved by experiment. This, however, may have been due to faulty methods. At present it is impossible to decide these disputed points. Nevertheless, we feel inclined to believe, from all the evidence which we have been able to obtain from the results derived from the study and treatment of the case, that the above explanation is possible and most probable and that we are dealing with a case of chlorid retention brought about by the action of some general toxemia which occasioned an increased permeability of the capillaries to chlorids and an augmented combining power of the protoplasm for these ions.

OCCURRENCE OF SPONTANEOUS ARTERIAL DEGENERATION IN THE RABBIT.*

By RICHARD M. PEARCE, M. D.

As one of the earlier investigators of lesions of the vascular system occurring in the rabbit after intravenous injections of adrenalin[1] I have been interested in the observation of Drs. Miles and Johnstone[2] concerning the frequent occurrence of spontaneous arterial lesions. These investigators suggest that the vascular lesions, ascribed by many observers to the injection of adrenalin, are in reality of spontaneous origin. In support of this view they present the results of the examination of a large num-

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[11] Bunge: Lehrbuch der physiologischen Chemie, Leipsic, 1900.

* Work done under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Am. Med. Assoc.*, 1908, li, 1056.

[1] *Jour. Exper. Med.*, 1906, viii, 74, 400; *Am. Jour. Med. Sciences*, 1906, cxxxii, 737.

[2] *The Journal A. M. A.*, Oct. 5, 1907.

ber of normal rabbits in which lesions similar to those produced by adrenalin occurred with equal or greater frequency.

The inevitable conclusion is either that the spontaneous lesions are common and that the individuals working with adrenalin have been careless about their controls, or that rabbits of certain localities, or those raised or kept under certain conditions, are peculiarly prone to spontaneous lesions. The first of these conclusions has been met by Dr. Joseph L. Miller,[8] who points out that in Jores exhaustive review of the many attempts, often on a large scale, to produce arteriosclerosis experimentally there is no mention of successful results. These experiments included the use of a variety of substances and in by far the larger number the rabbit was used.. Furthermore, during the past few years many attempts have been made to produce arterial lesions by subcutaneous and intraperitoneal injections of adrenalin as controls of the intravenous administration; a procedure necessitating a very careful comparative study of the rabbit's vascular system.

The only spontaneous lesions, according to Miller, which were described previous to the work of Miles and Johnstone were the slight changes described by Fisher in poorly nourished animals, a single instance reported by Ophüls and possibly the atheroma, in two rabbits, ascribed by Croftan to injections of hypoxanthin. Miller, moreover, points out that in Loeb's series of 100 normal rabbits and Meronescu's of 300, no lesions were found and also that the subcutaneous adrenalin injection experiments of Miles and Johnstone are of no value. The weight of evidence, therefore, does not support the suggestion that spontaneous lesions are general but have been overlooked by the neglect of control observations.

In this respect, however, I must admit my negligence in not reporting control observations in my earlier communication. Control observations were made on a small number of animals with entirely negative results, but on account of the small number were not published. During the past winter, in order to determine the incidence of spontaneous lesions in the rabbits supplied to the Bender Laboratory, I have examined sixty-two animals. Except for six pairs obtained from dealers in Pittsfield and Brookline, Mass., these animals were procured in the neighborhood of Albany, usually in small lots of one, two or three pairs, and in large part were animals which had been caught in the fall and domesticated but a short time. Of these, fifty-one may be considered presumably normal animals in that they had not been used previously for experiment of any kind, or were used only on the day of killing for blood pressure experiments or to obtain blood or fresh organs. They also represent animals which, in that they were used shortly after purchase, did not pass through a long laboratory life. They may be grouped roughly according to size into three groups of about equal number as large, small, and medium size. Vascular lesions were found in but three; these consisted, in each, of a few minute patches at the beginning of the aorta. All were large animals and presumably full grown.

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[8] *The Journal A. M. A.*, 1907, xlix, 1789.

Of the remaining eleven animals, one suffered from an abscess of the hip; three had received repeated injections of dog's serum; one, nephrotoxic serum; one, human blood; one, typhoid bacillus and three, chrome salts. These were all in the laboratory for several weeks or months. In this group lesions of the aorta occurred in four; in the animals receiving, respectively, injections of typhoid bacillus, dog serum, nephrotoxic serum and human blood. In two of these the lesions were diffuse involving irregularly the entire aorta and comparable to those produced by adrenalin. In the other pair a few small areas were present at the beginning of the aorta only.

This control study shows that spontaneous lesions were found in three of fifty-one presumably normal rabbits or in practically six per cent., or, if the animals used for various experimental purposes are included, in seven of sixty-two animals or eleven per cent. This last view, however, is hardly fair, for as the lesions were present in four animals of the second group, or in thirty-six per cent., it cannot be denied that the experimental procedure may possibly have had some share in their production. Certainly the influence of typhoid toxin and alien sera can not be entirely set aside in view of our knowledge of the very general degenerative changes which these substances cause.

In this connection it may be mentioned that Israel[4] in his study of the relation of heart hypertrophy to experimental nephritis has described and pictured a very diffuse lesion of the aorta in a rabbit receiving injections of alcohol directly into the kidney. This observation has been quite generally ignored in the recent literature of experimental arteriosclerosis; but Israel's illustration plainly pictures a lesion of the aorta not to be distinguished from that caused by adrenalin.

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[4] *Virchow's Archiv.*, 1881, lxxxvi, 299.

It would appear, therefore, that while spontaneous arterial degeneration may occur in the rabbit, it is not as constant a condition in all localities as the investigations of Miles and Johnstone indicate. Moreover, the figures here presented offer a satisfactory control of my earlier report on the general subject of experimental arteriosclerosis due to adrenalin and the later report in which I conclude that single doses of adrenalin may cause arterial lesions, a conclusion which might appear doubtful if viewed only in the light of the experiments of Miles and Johnstone.

In my opinion the occurrence of spontaneous lesions in the rabbit does not diminish the importance of the lesions due to adrenalin, but on the contrary, increases their importance, as an example of a lesion occasionally occurring naturally, but which may readily be produced experimentally. The rabbit thus becomes a peculiarly valuable animal for the study of vascular lesions, for the interest of the adrenalin lesion lies not so much in its arteriosclerosis-like nature as in the opportunity offered for the study of degenerative and reparative lesions of arteries.

The possibility of a variety of factors operating to cause vascular injury is suggested by the four positive findings in the second group of eleven rabbits. The contrast with the first group is very striking and would indicate that a study of the arterial system of a large number of rabbits, kept under a variety of conditions, and subjected to various experimental procedures, would yield results of great value concerning chronic vascular lesions.

Finally it may be stated that the demonstration of these spontaneous lesions in no way vitiates the importance of the experimental lesions but does demand a very careful control study of the rabbits in each locality in which experiments are made.

THE EFFECT OF CONDITIONS UPON THE LATENT PERIOD AND RATE OF ASEPTIC POST-MORTEM AUTOLYSIS DURING THE FIRST TEN HOURS.[1]

By HOLMES C. JACKSON.

Adjunct Professor of Physiological Chemistry, Albany Medical College.

The experiments about to be described had for their purpose an attempt to determine the character of the initial physical or chemical changes which occur in an organ as the result of its becoming disconnected from the blood supply, and are responsible for the setting up anew or the gaining ascendancy of those catalytic processes commonly known as autolysis. It seemed that information gained in this direction would be of especial value in a discussion of the question as to whether autolytic processes present but a survival of the same or similar processes occurring in the living cell or whether they represent reactions set up *de novo* as the result of incipient somatic death.

The point of attack in such a problem must fall upon the initial or early hours of the autolytic process. On this account, one may neglect in the discussion the almost numberless investigations dealing with autolytic processes in general and the effect upon them of changes in condition such as reaction, etc., and confine oneself to the experiments in which the autolysis was studied with especial reference to the first six to eight hours after shutting off the circulation from the organ either by removal from the body or otherwise.

But few investigators have busied themselves directly with this line of work. Of first importance must be considered the work of Lane-Claypon and Schryver (1) which indicates that the course of autolysis in the first twenty-four hours may be divided into three stages; (*a*) a latent period of from two to four hours, (*b*) a period of rapid autolysis and (*c*) a period of gradual autolysis.

Of perhaps chief interest in this connection is the latent period of two to four hours existing between the removal of the tissue from the body and the commencement of autolysis. If such a latency in autolysis does exist and is not the result of some condition of the experiment, then it becomes natural to conclude that this latent period represents the time during which the condition of the cell is being so changed by the lack of circulating blood and perhaps other causes that new or more rapid catalytic reactions may take place and set up a disintegration more pronounced than occurs during cellular life. Such reactions may be originated in various ways. Lane-Claypon and Schryver found that the state of nutrition markedly influenced the course of the autolysis in that the latent period was absent in the livers of fasting animals and that these tissues underwent more rapid decomposition than was the case in the well-fed animal. This is explained with the assumption that since it is probable that enzymes are liberated in the process of autolysis, the fasting liver contains more enzymes free to act (uncombined) or in the form of corresponding zymogen. The latent period is taken as indicating that in the well-fed animal a preponderance of the enzymes are in the form of zymogens and that the first stage in autolysis consists in the transformation of zymogen into active zymin. The presence of free enzymes in fasting animals indicates to these authors the probability that the liberation of these enzymes acts as a normal mechanism for the *intravitam* utilization of proteins in tissues—the supplying of food when none is taken in per os.

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[1] Conducted under a grant from the Rockefeller Institute for Medical Research. Read by title before the American Society of Biological Chemists, Chicago, Ill., January 2, 1908. Abstract appeared in the *Journal of Biological Chemistry*, 1908, 4, Nos. 4 and 5, p. xxxvii Received for publication October 12, 1908.

In a subsequent paper (2) Schryver has somewhat altered his theory of enzyme liberation as a cause of the latent period in order to correspond to criticisms of Wiener (3), who claimed that the latent period was merely due to the natural inhibitory effect of the alkaline reaction of the living tissues and that the latency ended with the sufficient neutralization of the alkalies by means of the acids formed in autolysis. This, of course, is reasoning in a circle since it does not explain what originates or accelerates the process by which the acids are formed for neutralization purposes.

Schryver has advanced a somewhat complicated theory for the preservation of chemical equilibrium in the living cell. The equilibrium of enzymes is established by the presence of an excess of ammonia which prohibits the formation of an acid reaction, necessary for autolysis. During starvation, the excess of ammonia gradually disappears and when the production of acid is sufficient to supersaturate the alkalinity, the autolytic enzymes liberate aminoacids; these in turn are transformed in the liver with the production of ammonia which again inhibits the autolytic processes. The non-nitrogenous moiety of the autolytic products serves as food for the fasting cells.

It can hardly be conceived that the author believes that free ammonia is present in the cell at any time, although this is necessary to the theory. In view of the neutrality of protoplasm and the extreme variations which may occur in the production of acid and of alkali without change in this neutrality as shown by Henderson and Black (4), Schryver's position seems untenable.

On account of the many possible explanations for the latent period and its importance in deciding the cause of autolysis, it seemed of sufficient interest to examine this subject somewhat more closely and to attempt if possible to shorten or prolong the period by altering the conditions of the experiment.

In order to obtain an insight into the character and velocity of the reactions taking place in the liver after its removal from the body, three factors were determined during the autolyses.

1. The changes in the depression of the freezing point. This method has been employed by several authors and more recently by Fredericqs (5), Delrez (6) and by Wells and Benson (7). The first of these investigators employed a somewhat complicated procedure in the preparation of the tissue for examination. The methods seem faulty and have been criticized by Wells. The latter two authors have determined coincidently the changes in the electrical conductivity and depression of the freezing point during autolysis. Both authors report that in general these factors parallel each other closely. In this work therefore the determination of the electrical conductivity has for various reasons been neglected.

2. The increase or decrease in noncoagulable nitrogen.

3. Changes in reaction were examined by means of phenolphthalein and dimethylaminoazobenzene. Body fluids react acid to the former and alkaline to the latter; phenolphthalein is particularly sensitive to changes in the hydrogen ionic content while dimethylaminoazobenzene only indicates an H^+ concentration about equal to that of an 0.8 per cent. lactic acid solution. In this way it seemed possible to determine the character of the substances causing the change in reaction, if such occurred.

The general method of experimentation was as follows: The liver tissue was removed aseptically,[2] passed through a sterile hashing machine into a sterile Erlenmeyer flask of 500 cubic centimeters capacity provided with a cotton plug. The flask containing 300 cubic centimeters of the salt solution (cold or at 38° C.) in which the autolysis was to proceed was counterpoised on scales and 100 grams of the ground tissue were weighed out by allowing the material to drop from the machine directly into the flask. During the process the whole apparatus was covered with a sterile cloth to exclude air contamination. The mixture being thoroughly shaken a control sample of 50 cubic centimeters was removed with bacteriological technique into a smaller stoppered flask. This was brought to the boiling point without change in reaction, allowed to cool, thoroughly mixed, and filtered.

This coagulum-filtrate was immediately put through the routine examination for determination of the depression of the freezing point by means of Beckmann's apparatus,[3] determination of the noncoagulable nitrogen by the Kjeldahl method and titration of the respective acidity by means of phenolphthalein and alkalinity to dimethylaminoazobenzene. For each of these determinations ten cubic centimeters of the filtrate were employed and all were conducted in duplicate.

After the removal of the control sample the flask was placed in the thermostat at 38° C; when the liver was not irrigated this occurred about twenty minutes after the death of the animal; the washing of the organ occupied ten minutes longer time. At definite times as indicated by the protocols, samples of 50 cubic centimeters were removed with bacteriological technique, the sample coagulated as above and the main flask returned to the incubator. At each time when a sample was withdrawn, a drop of the autolytic mixture was allowed to fall upon a sterile agar slant and at the end of the experiment these were incubated at 38° C. for from twenty-four to forty-eight hours. In practically all cases where the experiments ran for only six to eight hours, the agar slants when examined by a stained smear gave negative results—indicating a practical absence of organisms or, at least, that they were in such small numbers that a drop of the mixture taken at random failed to include one of them. All experiments in which the slant or smear indicated organisms, have been excluded. In the experiments where the period was extended, it was noticed that at times at the twelfth hour there was evidence of the presence in small numbers of certain organisms. In some instances the tests would remain negative even at twenty-four hours; in others the hay bacillus or another bacillus which will be discussed in a short note by Jackson and Hawn, made its appearance between twelve and twenty-four hours in quantities sufficient to give decidedly sour nonputrefactive odor to the autolytic mixture. In this connection must be mentioned the work of Magnus-Levy (8) who showed that acids of fatty nature as well as methane and hydrogen sulphide are produced during the first twenty-four hours of aseptic liver autolysis. His results as regards acidity are confirmed in the work presented here. This author also experienced the same difficulty in obtaining sterile organs that was met with in this work. Experiments in which infection has occurred have either been omitted or a note of the infection made in the protocol. In some other experiments a decided putrefactive odor appearing between six and eight hours indicated contamination of some sort; no account has been taken of these.

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[2] The usual surgical operative technique was employed.

[3] Several control examinations were made as to the depression of the freezing point of the coagulated and uncoagulated samples. The two gave results which were almost identical or within the limit of accuracy of the work.

Note must also be made of the fact mentioned by Schryver (9) and others that very frequently the glycogen when present in the liver of the dog disappeared very slowly during the autolysis. In certain experiments it was still present at the end of six hours of incubation; at times, however it would disappear earlier, but no instance can be found in the notes where the first or third hour sample was negative when the control indicated the presence of glycogen. Schryver states that in fasting dogs the glycogen disappears very quickly, while it remains for twenty-four hours in the livers of well-fed animals. It is hard to explain why livers of animals which have fasted for several days should contain glycogen at all, since it is ordinarily believed that in starvation it disappears quite quickly. In only some of the fasting animals in the experiments of this paper did glycogen appear in the liver; it is therefore manifestly impossible to make comparison with Schryver's results. The variations in appearance of glycogen and the rapidity of its disappearance noticed in the well-fed animals renders Schryver's distinction improbable however. The probable relationship of the slow disappearance of glycogen from the liver post-mortem and of its presence or absence to the autolytic processes going on, is discussed elsewhere in this paper.

Again in certain autolyses the mixture after the second or fourth hours began to take on a greenish nuance which developed quite rapidly in intensity until at the sixth hour, the color became dark green, almost black. This was noticed, of course, in a comparison of the coagulum-filtrates at the end of the experiments and seemed most prone to occur in those cases where the liver contained glycogen; the phenomenon remained present throughout the autolysis. Without doubt this peculiar condition was the result of the presence of oxidizing enzymes similar to tyrosinase and to those which noticed in plants by Palladin (10) and others, transform colorless into dark colored compounds, pigments or melanines.

As evidence of the accuracy of the experiments and the limits of error which the technique involved, reference must be made to the protocols of two experiments No. 25A, B and C and 26A, B and C.[4] In these cases three controls were simultaneously started the only difference being that two of them in each experiment were kept in the dark. Since this condition did not seem to effect the autolyses, the results serve as admirable controls of the method.

The experimental evidence obtained as the result of this work will be taken up as follows:

1. Effect on latent period of (*a*) condition of animal, (*b*) presence or absence of blood, (*c*) temperature of diluent salt solution.

2. Effect of conditions upon the commencement and rate of the autolysis. (*a*) nutritional state of the cell, (*b*) light, (*c*) antiseptics, (*d*) reaction, (*e*) salt concentration.

LATENT PERIOD.

Effect of Nutrition.—Schryver's experiments indicated that the best conditions for obtaining a latent period were present in the livers of well-fed animals. Hence Series I (four experiments) was carried out after the general method indicated previously in the paper. The animals were well-fed for several days previous to death; the livers were taken out without irrigation and *cold* physiological salt solution ($\Delta=0.568$) added in appropriate amount. The whole mixture of tissue and salt solution was then placed in the thermostat at 38° C. All experiments (5a, 5b, 6, 10) showed (Table I) that the depression of the freezing point

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[4] See Tables II, III and IV.

TABLE I.[5]

Series I

Liver Unwashed; Cold Saline Solution	Control	1 Hours	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours	7 Hours
Exp. 5a Well-fed	0.670 6.20 0.55 0.85	0.655 5.20 0.60 1.00	0.665 5.25 0.65 1.15	0.680 5.05 0.70 1.30	0.690 5.35 0.75 1.45	0.715 5.95 0.85 1.65	0.750 6.60 1.85 2.20	
Exp. 5b Well-fed	0.670 — 0.30 1.00	— — 0.40 1.05	0.665 5.65 0.40 1.00	0.665 5.75 0.35 0.95	0.685 5.55 0.55 1.00	0.685 5.55 0.60 1.00	0.695 5.65 0.65 0.95	0.710 5.85 0.70 0.95
Exp. 6 Well-fed	0.665 7.00 0.50 1.20	0.650 6.15 0.50 1.10	0.660 5.90 0.50 1.15	0.655 6.60 0.60 0.95	0.665 7.80 0.65 0.90	0.665 8.00 0.80 0.95	0.675 8.30 0.85 0.95	0.690 — 0.90 1.00
Exp. 10 Well-fed	0.675 7.45 0.75 1.35	— — —	0.660 6.85 0.90 1.40	0.660 7.35 1.05 1.25	0.675 7.60 1.05 1.35	0.685 7.85 1.10 1.30	0.720 7.60 1.30 1.55	0.725 7.70 1.35 1.40

Series II

Exp. 14 Not fed	0.600 7.35 0.75 1.35	0.595 7.45 0.90 1.40	0.605 7.70 1.05 1.25	0.615 7.75 1.05 1.35	0.615 7.85 1.10 1.30	0.620 7.90 1.30 1.55	0.645 8.45 1.35 1.40
Exp. 22 Not fed	0.660 6.95 0.40 0.90	0.685 7.20 0.50 0.95	0.710 7.10 0.70 1.00	0.700 6.90 0.70 0.90	— 7.20 0.95 1.05	0.710 7.20 0.90 1.10	0.715 7.10 1.10 1.00
Exp. 28A Not fed	0.235 5.80 0.40 1.35	0.235 4.65 0.55 1.15	0.240 4.55 0.45 1.25	0.290 4.35 0.60 1.20	0.330 4.45 0.85 1.25	0.340 4.40 1.05 1.10	0.345 4.55 1.35 1.35
Exp. 19 Well-fed	0.670 5.95 not done	0.710 6.00	0.720 5.75	0.725 5.75	0.735 6.00	0.755 6.30	0.790 7.50

remained practically the same as the control with a slight tendency perhaps to decrease until the third or the fourth hour after which a more or less marked increase occurred to the end of the experiment. The figures for the non-coagulable nitrogen although somewhat fragmentary indicate also a positive decrease from the control occurring during the first three or four hours. The figures for the fifth and sixth hours rising above the control are indicative of the commencement of nitrogenous autolysis. The acidity to phenolphthalein increased without much evidence of latency except in Experiment 6 while the figures for the alkalinity to dimethylaminoazobenzene vary—two experiments showing no change, one an increase and one a decrease. The figures considered as a whole would certainly convey the impression that autolytic changes of the usual type had not begun to show themselves until between the third and fourth hour after removal of the tissue from the animal's circulation.

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[5] The upper left-hand figures represent degrees of depression of the freezing-point; the upper-right hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

In the endeavor to control the statement of Schryver that the fasting livers did *not* show this latent period, Series II of three experiments (14, 22, 28A) were conducted in a manner similar in all details to Series I except that the animals were fasted for a few days previous to use. The livers were free from glycogen with the exception of that used in Experiment 28A.

In the protocol (Table I) the results for the depression of the freezing-point show that in two experiments a latent period of two hours existed while in the third (Experiment 22) autolysis began immediately. The figures for non-coagulable nitrogen in Experiments 22 and 28A however, point strongly to an inhibition of autolysis which lasted for five hours. In Experiment 28A the animal had not received food for three days previously; the liver contained glycogen which however gradually disappeared until no evidence of it could be obtained at the fourth hour, at which time it will be noticed that the marked depression of the freezing-point stopped. The non-coagulable nitrogen of the successive samples showed a marked diminution over the control with no evidence of an increase—rather a decrease—to the end of the experiment. This peculiar relation of glycogen disappearance to changes in the depression of the freezing-point and non-coagulable nitrogen will be taken up later in the paper. Finally one experiment (19) with a well-fed animal similar to those of Series I gave no latent period as indicated by the depression of the freezing-point but the non-coagulable nitrogen figures showed an inhibition of autolysis lasting until the fourth hour. In all of the experiments in Series II the acidity figures with phenolphthalein showed a consistent increase from the very beginning of the experiment, while the alkalinity to dimethylaminoazobenzene remained constant to the end.

Although Series I with well-fed animals resulted as expected according to Schryver, Series II with three fasting animals and one well-fed animal was unsatisfactory.

Turning about to find a cause for these varying results and at the same time attempting to obtain some condition which might influence the latency of the autolysis, it seemed plausible to try the effect of two factors; first, the absence of blood; and second the use of *warm* (38° C.) saline at the outset of the experiment.

Effect of Blood.—The elucidation of the question as to the effect of blood upon the latent period would bear directly upon the criticism of Schryver by Wiener mentioned above, as well as serve to accentuate the fact of the well-known inhibitory effect of blood upon the rapidity of autolysis noticed so frequently[6] although its cause is so poorly understood (11). The washing of the alkaline blood from the liver would tend certainly to remove a certain amount of bases from the organ together with other salts lost by diffusion during irrigation with the salt solution. Consequently two experiments (Series III) were conducted in which the livers were thoroughly irrigated through the portal vein with cold saline solution and diluted with cold saline solution; one animal was fasting (20) and the other well-fed (17). From the figures (Table II) for the depression of the freezing-point no latency of autolysis occurred and the increase is pronounced to the end of the experiment. The same is true for the non-coagulable nitrogen except that a slight indication of possible latency showed itself in the well-fed animal. The acidity to phenolphthalein increased and the alkalinity to dimethylaminoazobenzene remained constant as usual.

These two preliminary experiments seemed sufficient to make it evident that the presence of blood formed one of the inhibitory factors in the latency. This fact is of course not new except as it applies to the latent period and was to be expected since, as was stated above, the inhibitory effect of alkalies upon autolysis and their supposed action in prohibiting autolysis *in vivo* might be considered as persisting some time after removal of the organ after death.

Effect of Temperature of Salt Diluent.—The next series (IV) was planned to determine the effect of keeping the organ at body temperature during removal and subsequent autolysis. The washing was therefore accomplished with *warm* saline and *warm* saline added as diluent. The only time during which a lowering of tem-

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[6] Schryver (p. 180), in one experiment, found no difference in the rate of autolysis between the perfused organ and one containing blood.

TABLE II.[7]

Series III

Liver Washed; Cold Saline	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 20 Not fed	0.555 5.40 0.35 0.70	0.570 5.90 0.40 0.65	0.590 5.80 0.70 0.70	0.595 6.10 0.75 0.80	0.600 6.30 0.80 0.85	0.610 6.40 0.95 0.80	0.625 6.60 1.05 0.90
Exp. 17 Well-fed	0.565 5.05 0.50 1.00	0.585 4.95 0.60 0.90	0.600 5.15 0.70 0.95	0.620 5.50 0.80 0.95	0.640 5.65 0.85 1.20	0.650 5.80 1.00 1.15	0.710 6.30 1.10 1.05

Series IV.

Liver Washed and Diluted with Warm Saline							
Exp. 9 Well-fed	0.575 5.70 0.50 1.15	0.595 6.35 0.85 1.20	0.605 7.05 1.15 1.40	0.620 7.35 1.15 1.50	0.635 8.65 1.25 1.50	0.665 9.65 1.35 1.50	0.670 10.50 1.60 1.95
Exp. 11 Well-fed	0.555 5.40 0.50 1.10	0.540 5.35 0.65 1.25	0.585 5.50 0.80 1.05	0.590 5.70 0.80 0.95	0.590 6.15 0.9 1.00	0.615 6.30 1.00 1.25	0.640 6.80 1.10 1.35
Exp. 15 Well-fed	0.615 6.30 0.40 1.00	0.605 6.10 0.55 1.00	0.615 6.20 0.60 0.95	0.635 6.35 0.75 0.95	0.640 6.50 0.90 1.00	0.645 7.20 1.00 1.25	0.670 8.25 1.10 1.35
Exp. 18 Well-fed	0.660 5.30 0.40 0.60	0.675 5.85 0.60 0.95	0.705 5.90 0.65 0.95	0.710 6.30 0.70 0.75	0.725 6.70 0.85 0.75	0.735 6.80 0.90 0.65	0.740 7.25 1.05 0.75
Exp. 29E Not fed	0.325 4.50 0.45 0.75	0.345 0.65 0.80	0.365 5.70 0.80 0.80	0.385 0.95 0.70	0.395 6.45 1.10 0.75	0.415 1.20 07.5	0.435 7.45 1.40 0.70
Exp. 26A Not fed Dark	0.560 4.75 0.35 060.	0.565 5.10 0.50 0.70	0.575 5.55 0.75 0.65	— 6.00 0.80 0.60	0.585 6.50 0.85 0.70	0.600 7.15 0.90 0.75	0.625 7.65 1.00 0.80
Exp. 26C Not fed	0.555 4.90 0.20 0.50	0.565 4.95 0.35 0.75	0.570 5.25 0.55 0.85	0.585 6.30 0.75 0.80	0.610 6.75 0.90 0.75	0.620 7.00 0.95 0.80	0.625 7.45 1.05 0.85

perature could occur was during the period of hashing. This, of course, represented only a few minutes and could cause at most a temperature depression of a few degrees. Some of the hashed material was tested and gave 34.5° C. The warm saline quickly brought this up to 37° C. Seven experiments were carried on in this way (Experiment 9, 11, 15, 18, 29E, 26A, 26C). Of these the first four were well-fed and the last three fasting animals. Of the well-fed animals two (9, 18) showed (Table II) a marked autolysis at the outset as indicated by the figures for the depression of the freezing-point and nitrogen. On the other hand in Experiments 11 and 15 a well-marked latent period was present although it persisted for only one hour. Only traces of glycogen were present in the liver of Experiment II and it was absent in Experiment 15. The fasting animals whose livers were irrigated and diluted with warm saline gave figures both for depression of the freezing-point and nitrogen indicating no latency and an autolysis which was the most marked of all the experiments of this type.

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[7] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower left-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

A fifth series of four experiments (25A, 25C, 31C and 36A) were conducted with unwashed livers of well-fed animals employing warm saline as diluent. Three showed (Table III) immediate autolysis both in the figures for depression of the freezing-point as well as for non-coagulable nitrogen; one (36A) did not autolyse during the first three hours according to the nitrogen figures,

TABLE III.[8]

Series V

Unwashed Liver Well-fed Warm Saline	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 25A Dark	0.730 5.10 0.30 0.65	0.745 5.40 0.50 0.55	0.775 5.60 0.60 0.65	0.790 5.70 0.65 0.80	0.810 5.80 0.75 0.90	— — — —	0.840 6.30 0.95 1.20
Exp. 25C	0.725 4.65 0.4 0.50	0.755 4.90 — 0.60	0.780 4.95 0.55 0.70	0.795 5.10 0.65 0.85	0.810 5.20 0.70 0.90	0.825 5.65 0.85 1.05	0.835 5.85 0.95 1.10
Exp. 31C	0.530 6.10 0.50 0.70	0.590 6.20 0.60 0.80	0.605 6.25 0.70 0.80	0.625 6.35 0.75 0.65	0.645 6.70 0.85 0.80	0.660 7.00 0.85 0.60	— — 0.95 1.35
Exp. 36A	0.720 6.05 0.40 1.50	0.715 5.60 0.70 1.30	0.735 5.50 0.75 1.15	0.755 5.90 0.80 1.25	0.775 6.15 0.85 1.20	0.785 6.65 0.85 1.10	0.800 7.15 0.85 1.20

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[8] The upper left-hand figures represent degrees of depression of the freezing-point the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

the depression of the freezing-point only indicating an inhibition for the first hour only. It is questionable whether an autolytic latency existed here.

The following classification of experiments in the five series will indicate the results at a glance.

Conditions of Experiments	Latent Period		
	Positive	Negative	
Unwashed, well-fed, cold saline	4	0	Series I
Unwashed, fasted, cold saline	2	0	Series II
Unwashed, well-fed, cold saline	1?	1	Series II
Washed, fed, cold saline	0	1	Series III
Washed, fasted	..	1	Series III
Washed, fed, warm saline	1	3	Series IV
Washed, fasted, warm saline	0	3	Series IV
Unwashed, fed, warm saline	1?	3	Series V
	7+2?	12	

Positive Latent Period

Fed	5+2?	Fasting	2
Cold saline	6+1?	Warm saline	1+1?
Unwashed	6+2?	Washed	1

From the tabulation it will be seen that out of twenty-one experiments nine showed a latent period; in two of these however the latency lasted only one hour so that these have been given a question mark. Of the nine positive experiments seven occurred with well-fed animals and only two in fasting ones. These results are somewhat in agreement with Schryver. Again seven of the positive latent periods occurred in experiments where cold saline was employed as diluent. Schryver employed small amounts (4 grams) of material for his experiments. This would cause a rapid lowering of temperature with consequent inhibition. Whether this author used a cold or warm diluent is not stated, and the organs were not washed.

Perhaps some importance may be attached to the fact that five of the nine positive results occurred as the first five experiments performed when the time between the removal of the organ and commencement of the autolysis was somewhat longer than in the latter experiments when our general technique had improved. In this connection it is proper to state that of twenty-five other and similar experiments reported below only four showed a latent period before autolysis and of these cold diluents were employed in three cases.

In view of these facts and of the fact that of thirteen latent periods, nine were in experiments where cold diluents were used, it is evident that the low temperature of the mixture acts as an inhibitory factor in causing a latent period of autolysis until the material becomes warmed throughout to body heat. The presence of blood in the unwashed organ adds an additional factor to the inhibiting forces.

Upon the whole, therefore, it seems that the latent period is most prone to appear in unwashed livers where cold diluent is employed and in those cases in which the animal was previously well-fed. It seems however, that in the light of all the experiments herein presented, it becomes questionable whether the feeding of the animal and the consequent condition of the liver possesses any direct influence on the latency of autolysis.[9] In this it is impossible to agree with Schryver nor does the latter's reasoning in regard to the liberation of enzymes in the fasting condition seem plausible. There does not exist at present, any evidence which points to any qualitative difference in the enzymic condition between the metabolism of well-fed and fasting animals. The statement that in fasting, autolytic processes by causing decomposition supply the needs of the body by the utilization of the degenerative products simply amounts to placing a well established fact in new terms, since it is very difficult to draw a sharp line between the normal analytic processes by which energy is liberated and those of autolysis associated with the death of the cell. It would appear that the question was more one of a disturbed quantitative equilibrium of the cell than of any qualitative enzymic differences.

EFFECT OF CONDITIONS UPON THE RATE OF AUTOLYSIS.

The previous discussion has had to do with autolysis within the first three or four hours after the removal of the organ from its circulation. The fact that the results indicated that the latent period was relatively inconstant and dependent upon a variety of factors led to the attempt to study first, the rate of autolysis within the first twelve hours and second, the effect upon it of altering certain conditions in the experiment in the hope that the onset of changes favoring autolysis might be inhibited. This consisted mainly in endeavoring to continue the alkalinity of the cell by means of alkaline phosphates.

Nutritional State of the Cell.—One of the most important factors to be considered in the elucidation of the origin and rate of autolysis consists in the determination of the level of equilibrium upon which the cell exists at the time of stoppage of the circulation. We look to the diet of the animal as one of the most ready means of normally altering this condition and yet it becomes one of the most difficult to control, since no two animals react similarly to diet or to fasting.

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[9] As explained later in the paper, the nutritional state of the cell may indirectly cause autolytic variations.

The fat content of the livers of normal animals under the same diet varies as greatly as does the power of individuals to lay on subcutaneous fat.

The appearance or absence of glycogen serves perhaps as best evidence concerning the condition of the cell from the standpoint of nutrition and it is usual to conclude that the tissues are actually in a state of undernutrition when the liver is free from glycogen. Well-fed animals usually possess organs containing more or less glycogen, but even here exceptions exist and frequently animals after a long period of excessive carbohydrate diet do not show glycogen in their livers.

Concerning variations in the nitrogenous content of the liver, it becomes more difficult to make definite statements. Pearce and Jackson (12) showed that as the result of incipient necrosis or starvation from lack of circulation the cells involved lay on nitrogenous compounds in the same way as they do fat. This was in agreement with the results of Seitz (13) obtained under normal conditions. Schryver states that the liver of a fasting dog contains more non-coagulable nitrogen than that of a well-fed animal. In the experiments here reported a great variation in the amount of initial non-coagulable nitrogen exists. The average figure for twenty experiments upon fasting animals compares within one per cent. of that for eighteen well-fed animals. Selecting two cases (Experiments 25 and 26) in each of which there are three controls it is evident that no difference exists. It is not possible therefore to confirm Schryver's statement in regard to differences in nitrogen.

From a consideration of the initial figures for the depression of the freezing-point in twenty-nine experiments in which physiological saline was employed as diluent it is evident that the fasting liver possessed the lowest concentration. Eleven washed organs of which six were fasting and five well-fed and eighteen unwashed organs, seven fasting and eleven well-fed gave averages as follows:

Washed, fasting	0.475°	(310–560)	Unwashed, fasting	0.609°	(575–660°)
Washed, well-fed	0.594°	(555–660)	Unwashed well-fed	0.664°	(515–735°)

These figures seem sufficiently definite to indicate that as far as ionic concentration is concerned the fasting animals[10] liver showed the lowest figures whether washed or unwashed. The maximum and minimum effects are indicated in Experiments 25 and 26. Experiment 25 was an unwashed well-fed liver and gave, $\Delta = 0.730$ (average three controls) while Experiment 26 with washed and fasting organs, $\Delta = 0.555$ (average three controls). In all instances the washing of the organ decreased the ionic strength of the tissue; this procedure seemed to have little effect however upon the initial acidity or alkalinity. From the fact that perfusion of an organ causes a decreased ionic concentration which is not paralleled by changes in reaction, it seems probable that the ionized substances in the cell which impart its so-called alkaline reaction are of such a character (ionized protein) that interchange or osmosis through the endothelium does not readily take place.

There are no data obtainable from the results presented in this paper which can be of service in explaining the effect of these variable nutritional conditions of the cell upon the latent period and rate of autolysis. The cursory outline above serves merely to bring to mind possible variations in cell equilibrium as regards the carbohydrates, fats, proteins, osmotic concentration, etc. This phase of the subject will receive further consideration in the final discussion as to the cause of and variations in the changes in the reaction of the cell occurring at its death.

Light.—The first external change in condition which usually occurs in tissues undergoing incipient autolysis *in vitro* and which is not in accordance with autolysis *in vivo* consists in the placing of the material in the light. Two experiments (25 and 26)— one a well-fed and the other a fasting animal—were consequently performed in which the liver was removed in the dark and two of the samples (25A and B and 26A and B)[11] autolysed in the absence of light. The third sample (25C and 26C) as control, underwent autolysis as usual. These experiments continued for seven and one-half hours. The results (Table IV) indicate that the presence of ordinary light exerts no appreciable influence upon autolysis. The increase of the depression of the

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[10] Animals were given water *ad libitum*.

[11] Experiments 25A and 26A differed from 25B and 26B in that in the former a warm diluent was employed. Experiments 26A and 26C appear as the last two upon Table II; Experiments 25A and 25C, as the first two in Table III.

TABLE IV.[12]

Autolysis in the Dark; Cold Saline (Control)	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 25B Not washed well-fed	0.735 4.80 0.40 0.65	0.755 5.50 0.50 0.70	0.765 5.65 0.65 0.85	0.780 5.85 0.60 0.80	0.810 5.95 0.65 0.85	0.820 6.00 0.70 0.80	0.835 6.10 0.75 0.85
Exp. 26B Washed; not fed	0.550 5.20 0.35 0.55	0.550 5.35 0.30 0.65	0.560 5.85 0.50 0.80	0.575 6.10 0.60 0.70	0.590 6.60 0.70 0.65	0.615 7.15 0.95 0.85	0.630 8.00 1.00 1.05
Washed; Not fed	Control	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	
Exp. 29E Warm saline	0.325 4.50 0.45 0.75	0.365 5.70 0.80 0.80	0.395 5.75 1.10 0.75	0.435 7.45 1.40 0.90	0.485 10.10 2.50 0.95	0.565 15.50 2.95 1.95	
Exp. 29F Warm saline and toluol	0.310 4.80 0.45 0.70	0.330 5.90 0.85 0.85	— — 0.80 0.85	0.385 6.45 0.85 0.90	0.390 7.40 0.90 0.85	0.395 8.00 1.05 0.90	
Unwashed; well-fed	Control	1 Hour	3 Hours	5 Hours	7 Hours	12 Hours	
Exp. 31C Warm saline	0.530 6.10 0.50 0.70	0.590 6.20 0.60 0.80	0.625 6.35 0.75 0.65	0.660 7.00 0.85 0.60	— 7.60 0.90 0.80	1.020 10.70 1.45 0.95	
Exp. 31B Warm saline and chloroform	0.515 5.35 0.5 0.90	0.530 5.80 0.60 0.85	0.600 6.25 0.70 0.80	0.620 6.70 — —	0.635 7.00 0.95 1.35	0.690 8.50 1.95 3.35	

freezing-point, increase of non-coagulable nitrogen and change in reaction ran parallel in both experiments. The differences which one experiment showed as against the other as the result of the feeding of the animal, will be considered later.

Antiseptics.—Autolytic experiments as usually conducted in order to insure complete asepsis entail the employment of antiseptics such as toluol, chloroform, etc. The results of Lang (14), while not very complete, indicate that germicidal agents are not without effect upon the activity of the enzymes in autolysis. Wells and Benson (7) however incline to the view that with certain precautions, chloroform may be employed without inhibitory effect. It is evident that where comparative results are to be obtained, this variable factor should be eliminated. In this work antiseptics were not employed except in Experiments 29 and 31. In the former toluol was utilized and in the latter, chloroform. A glance at the figures in the tables will be sufficient to indicate the inhibitory action of the antiseptic, apparently more potent in the case of toluol than of chloroform. This is evident both in the figures for the depression of the freezing-point and for the non-coagulable nitrogen. Experiment 29 ran for ten hours during which time the depression of the freezing-point increased in the mixture without toluol from 0.325° to 0.565°; while in the toluolized autolysis it increased from 0.310° to 0.385°. In Experiment 31 the similar figure for twelve hours duration are with chloroform 0.515° to 0.690°; without chloroform 0.530° to 1.020°. The nitrogen increase paralleled them closely.

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[12] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of $N/10$ acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of $N/10$ acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of $N/10$ alkali.

Reaction.—It has been quite definitely decided as the result of the work of many investigators (15) that acids accelerate and alkalies inhibit the rate of autolysis. In the majority of the experiments conducted by these workers a concentration of H^+ or OH-ions has been employed which is out of all accord with that possible in the cell of the animal body. The blood and protoplasm are from the standpoint of physical chemistry considered as neutral (4); very slight variations from this condition may cause profound alterations in the general metabolic process. It seemed therefore, of more value from a comparative standpoint to attempt to vary the so-called acidity and alkalinity relations of the cells in ways which more closely simulate the normal.

The immense importance which the phosphates play as regulating mediums for reaction in the body has been of late repeatedly emphasized. Mixtures of the mono-hydrogen and dihydrogen salts may be appropriately made so that the resultant solution is either neutral, alkaline or acid.[13] Hence disodium monohydrogen phosphate was employed as diluent in the hope of increasing the "alkalinity" of the tissue while the dihydrogen monosodium phosphate promised to augment the "acidity." A further method employed for the latter purpose consisted in the addition of pure neutral ethyl butyrate to the autolytic mixture. As autolysis proceeded the lipolysis of the butyrate set free butyric acid, thereby increasing the acidity markedly. This reaction may also be supposed to take place in the living cell but ordinarily sufficient bases are at hand for neutralization. In autolysis (lipolytic) should the bases be lacking the H + · concentration would be increased.

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[13] In relation to phenolphthalein. Henderson (4) has shown that in solutions of these two salts great variations in their relative proportions may exist without changing the $H+$ concentration to any great degree.

An examination of the figures obtained for the control samples as indicative of the character of the initial state of reaction of the tissue indicates that either the method of titration with the two indicators is too crude to show slight variations which might occur in the living tissue, or the factors which influence the reaction of the tissue and which would aid in explaining the results, are unknown. Certain differences in the figures for the controls under the various conditions did appear but no one condition which has been discussed here is apparently accountable for the changes.

In Experiments 23, 28B, 30A, 32C, 33B and 36 (Table V) attempts were next made to increase the alkalinity of the reaction of the mixture in which autolysis was to occur by means of disodium hydrogen phosphate in five per cent. solution and Experiment 28C by alkaline Locke's solution.[14] It is interesting to note that while the disodium phosphate was *alkaline* to phenolphthalein (0.8 c.c. $N/10$ acid for 10 c.c. of solution) and alkaline to dimethylaminoazobenzene (10.65 c.c. $N/10$ acid for 10 c.c. of solution), when the autolytic mixture of this solution and tissue was analyzed, the mixture possessed the *acidity* to phenolphthalein ordinarily found when sodium chloride is employed as diluent. Unfortunately, it is impossible to say from the methods employed just what physical changes occurred when the tissue and phosphate solution were mixed. From the chemical standpoint of reaction the tissue transformed the alkaline solution (phenolphthalein) to one which reacted acid. The explanation for this probably lies in the rearrangement of phosphates in the solution by which the large excess of disodium hydrogen phosphate reacted with acid factors in the tissues and became transformed into sufficient dihydrogen sodium phosphate to cause the autolytic mixture to assume its normal reaction. This forms simply another manifestation of the regulating mechanism described by Henderson (4). All attempts therefore to increase in this manner the alkalinity (phenolphthalein) were negative and the results

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[14] Locke's solution to which was added sufficient sodium bicarbonate to bring the strength of the salt up to 0.5 per cent.

TABLE V.[15]

5 Per Cent. Na_2HPO_4.	Control	1 Hour	3 Hours	6 Hours	8 Hours	10 Hours
Exp. 23 Washed; well-fed; cold diluent	0.525 — 1.45 11.50	0.520 5.30 1.90 11.35	0.560 5.60 2.00 11.30	0.610 5.80 2.25 11.80		
Exp. 28B Unwashed; not fed; warm diluent	0.530 4.30 0.65 11.45	0.545 5.60 1.00 11.25	0.615 7.10 1.40 11.40	0.640 7.75 1.65 11.80		
Exp. 30A Unwashed, not fed; 10 *per cent.* warm diluent	0.685 6.70 0.70 21.75	0.710 6.65 1.00 21.65	0.745 6.50 1.05 20.90	0.780 7.65 1.15 20.95	0.795 — 1.70 20.05	0.900 12.45 2.40 19.50
Exp. 32C Unwashed; not fed; cold diluent	0.735 — — —	0.705 — — —	0.705 — — —	0.715 — — —		
Exp. 33B Unwashed; not fed; cold diluent	0.700 8.55 0.90 10.3	0.730 8.15 1.10 10.6	0.740 8.20 1.60 10.1	0.790 8.80 2.50 9.65		
Exp. 36 Unwashed; well-fed warm diluent	0.910 6.15 0.90 13.1	0.900 6.40 1.2 14.9	0.950 6.90 1.55 13.05	0.995 7.55 1.75 12.65		1.620 17.55 17.55 26.4
Exp. 28C Unwashed; not fed; warm *Alkaline Locke's solution*	0.680 5.60 1.60 1.15	0.700 4.40 1.70 1.15	0.785 4.65 1.85 —	0.795 4.80 1.7 1.50	0.805 4.60 1.75 1.25	
Exp. 32B Unwashed; not fed *Cold Na_3PO_4*	0.650 — — —	0.660 — — —	0.650 — — —	0.650 — — —		

of these experiments do not differ from those reported with saline as diluent.

One experiment performed with Locke's solution made alkaline with 0.5 per cent. sodium bicarbonate[16] (28C) ran seven and one-half hours. In this instance also the resultant mixture of liver and bicarbonate solution became acid to phenolphthalein and alkaline to dimethylaminoazobenzene. In fact the respective acidity and alkalinity was greater in each case than with sodium chloride. Undoubtedly a reaction occurred between the phosphates of the cell and the sodium bicarbonate, carbon dioxide being liberated, and in this way increasing the acidity to phenolphthalein.

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[15] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

[16] Of this solution, 10 c. c required 0.15 c.c *N*/10 acid to neutralize to phenolphthalein and 1.55 c.c. to dimethylaminoazobenzene.

The increase in depression of the freezing-point[17] was about that observed in other experiments, where a similar reaction was present; no inhibition or latent period could be noticed. An examination of the figures for non-coagulable nitrogen indicates however that no nitrogenous autolysis occurred, the figures for the end of the experiment being the same as the control or even somewhat lower. In this case no increase in acidity (phenolphthalein) took place such as ordinarily occurs with sodium chloride solution as diluent.

One experiment employing tri-sodium phosphate as diluent did not result favorably since the autolytic mixture became extremely thick and ropy. Upon heating no coagulation occurred; the mixture required the addition of such a large amount of acid before complete coagulation occurred that attempts to perform nitrogen and acidity determinations were abandoned. Unfortunately the diluent solution was employed cold so that it is impossible to decide whether the extremely long "latent" period as evidenced in the depression of the freezing-point was to be ascribed to this or to the phosphate solution. It would seem more probable that the lack of increase in molecular concentration found in this autolysis was due to the phosphate solution on account of its alkalinity (phenolphthalein) and this fact agrees with observations of previous investigators that alkalies inhibit autolysis. An alkalinity equivalent to this never occurs in the body.

In one experiment (29D) where dihydrogen sodium phosphate served as diluent, the autolytic mixture was strongly acid to phenolphthalein. This experiment should be compared with Experiment 29E (Table II, Series IV) and the control with saline. No noticeable variation in rate of autolysis can be detected.

In Experiment 33 and 36 in which pure ethyl butyrate was added to the autolytic mixture a most marked increase in acidity (phenolphthalein) was observed together with the greatest augmentation of non-coagulable nitrogen and the depression of the freezing-point obtained in any of the experiments. These two experiments ran for twelve hours and were absolutely sterile throughout. The depression of the freezing-point increased in Experiment 36 from 0.810° to 1.515° and in Experiment 33 from 0.685° to 1.285°. The non-coagulable nitrogen rose in Experiment 36 from 5.8 to 28.15 and in Experiment 33 from 3.25 to

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[17] Whether this is indicative of autolysis is questionable; *c. f.*, the later discussion on this point.

TABLE VI.[18]

	Control	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Exp. 29D Washed; not fed; 5 per cent. H_2NaPO_4	0.635 5.05 10.95 1.85	0.635 5.30 11.7 1.75	0.680 5.50 12.85 1.95	0.725 7.40 13.05 1.75	0.765 12.40 13.50 1.60	0.795 14.35 14.05 1.65
Exp. 33C Unwashed; not fed; 1 c.c. ethyl butyrate with saline diluent	0.685 3.25 1.10 2.00	0.725 4.50 1.30 2.10	0.745 7.40 1.85 2.45	0.820 14.90 3.00 2.80	— — — —	1.285 33.85 5.10 8.60
Exp. 36C Unwashed' fed; 1 c.c. ethyl butyrate with saline solution	0.810 5.80 1.25 1.10	0.815 5.60 1.55 1.55	0.845 5.35 1.60 1.45	0.920 10.05 2.35 1.65		1.515 28.15 6.65 5.35
Exp. 27E Unwashed; not fed; warm Locke's solution.	0.625 6.25 0.40 0.75	0.650 6.10 0.60 0.70	0.670 6.10 0.80 0.70		0.705 6.50 1.00 1.00	
Exp. 31A Unwashed; well-fed; warm Locke's solution	0.630 5.60 0.60 0.40	0.720 5.65 0.75 0.75	0.775 5.60 0.85 0.75		0.800 7.20 1.15 0.85	1.015 20.8 6.80 2.7

33.85.[19] Considered from every standpoint the autolysis was most strikingly accelerated by the formation of the butyric acid during the progress of the autolysis.

In general therefore attempts to alter the rate of autolysis by means of acid and alkaline phosphates and bicarbonates resulted negatively. Some evidence was obtained that an alkaline reaction tends to inhibit the nitrogenous autolysis; this was especially well marked in Experiment 28C. The production of butyric acid during autolysis set up a marked acceleration in the rate of the decomposition.

Salt Concentration.—It seemed plausible that one of the conditions which favored the onset of autolysis might consist in the decrease in concentration of the salts (mainly calcium and potassium compounds) of the tissue as the result of the dilution with sodium chloride and phosphates. Such a condition would of course be accentuated in a perfused organ since during the irrigation the calcium, potassium, and other salts would diffuse out from the cell into the perfusing solution.

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[18] The upper left-band figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of $N/10$ acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of $N/10$ acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of $N/10$ alkali.

[19] In Experiment 36 it is noticeable that the acidity did not increase very rapidly during the first four hours and that the nitrogenous autolysis suffered a latent period.

In order to partially avoid such diminished concentration, in two experiments (27E and 31A) Locke's[20] solution was added as diluent and the autolytic rate studied. Although the results show an increase in ionic concentration, the figures for the non-coagulable nitrogen are plainly indicative of a lack of autolysis existing up to the fifth hour. While one cannot draw too definite conclusion from the results of only two experiments, it seems reasonable to believe the retaining of the salt content of the tissue in approximately unchanged concentration, acts as another factor tending to inhibit or at least to retard nitrogenous autolysis. It is also probable that the Ca or K ions are in some way active in this regard, and that the difference in rate of autolysis noticed between washed and unwashed organs can be ascribed to this cause in part.

This question was attacked in another way. The tissues were aseptically removed and allowed to autolyze *en masse* in the thermostat and then diluted as usual with three volumes of physiological saline. Unfortunately no figures for non-coagulable nitrogen were obtained in this series.[21]

The depression of the freezing-point for the tissue itself and the diluted mixture increased in about the same rate as in all other experiments.

DISCUSSION.

The two procedures employed for the determination of the inception and rate of autolysis have been utilized previously by several investigators. The increase in non-coagulable nitrogen was the first test applied in this direction since it was early recognized that in the autolytic hydrolysis the coagulable nitrogen of the protein became changed into nitrogen of substances which were of smaller molecular weight and could not be rendered insoluble by heat. More recently however the attempt to control this procedure by other methods has resulted in the determination of the electrical conductivity and of the molecular or ionic concentrations of the solutions undergoing autolysis. If we are dealing with autolytic mixtures of pure protein, hydrolytic changes occurring in the solution would make themselves evident by all three methods, but not simultaneously, since in the initial stage of the reaction the proteins would become transformed into proteoses or non-coagulable nitrogen, without any decided augmentation in molecular or ionic concentration sufficient to effect the depression of the freezing-point or electrical conductivity. Toward the end of autolysis the maximum proteose nitrogen might be reached while progressive hydrolysis would continue to break down the molecules still further with consequent increased molecular concentration thereby affecting the depression of the freezing-point. The electrical conductivity on the other hand could only be increased by the formation of ionized molecules. From this it is evident that even in a simple solution of protein these three factors might not run parallel.

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[20] When physiological saline is employed as diluent, the osmotic concentration of the tissues is supposed to continue the same as when the blood is circulating through the organ. The percentage concentration of the salts other than sodium chloride is nevertheless markedly diminished. Locke's solution which approaches the blood as regards its content of inorganic salts was utilized for this reason.

[21] For this reason the study of this type of experiment is to be continued more particularly with reference to possible differences in the rate of autolysis after the organ has been prepared by perfusion *in situ* with solutions of various types of salts, and in this way the attempt may be made to alter the conditions existing in the cell before the commencement of autolysis.

In the cell however the process becomes still more complex. Autolysis of non-nitrogenous substances such as glycogen, the lipoids, neutral fats and the rearrangement of inorganic salts would set up changes in molecular and ionic concentration which would not be indicated by a study of variations in non-coagulable nitrogen. It is hard therefore to agree with the statement of Wells that determinations made of these three factors (non-coagulable nitrogen, depression of the freezing-point and electrical conductivity) parallel one another. That they might do so must be admitted; that the chances are very much against their doing so is most probable.

A general survey of the results obtained in this investigation presents much evidence in favor of the latter view. In some experiments (5b, 10, 22, 23, 27E and 28A and 28C) conclusions would be reached from the figures obtained from the non-coagulable nitrogen that no autolysis had occurred up to the sixth or eighth hour. In fact in Experiments 28A and 28C less non-coagulable nitrogen was present in solution at the end of seven and one-half hours than in the control at the outset of the experiments. One could naturally assume that non-coagulable nitrogen had become synthetized into protein nitrogen. The figures for the depression of the freezing-point, however, show that the molecular or ionic concentration was increasing gradually up to the end of the experiments. This is especially well marked in

Experiment 28C, where depression of the freezing-point increased from 0.680° (control) to 0.805° (seven and one-half hours). Evidently non-nitrogenous molecules were undergoing hydrolytic cleavage with the production of smaller and more numerous molecules.

We do not have to look far for an explanation of these results. It has been mentioned elsewhere that with apparently the same conditions of diet, the liver of dogs varies markedly in the content of fat and of glycogen and there is also variation in the rapidity with which the latter disappears. With these points in mind a study of the notes taken in various experiments plainly brings out the fact that in those cases where the glycogen disappeared most rapidly as deduced by the decrease in opalescence of the filtrate after heat coagulation, the depression of the freezing-point tended to increase regardless of changes in non-coagulable nitrogen. In the absence of glycogen the depression of the freezing-point was not affected in this manner. Evidently the increased depression of the freezing-point occurred in greatest part at the expense of the hydrolysis of glycogen, the latter being transformed into smaller molecular compounds, such as maltose, lactic acid, etc.

Concerning lipolytic changes, it becomes more difficult to determine what part these processes are playing in the whole general autolytic change, since there is no way of visually following the transformation as is the case with glycogen. Increased acidity in the autolytic mixture may be the result of the hydrolysis of fats or equally well of the carbohydrates. It therefore is of the utmost difficulty to decide to what process is due the increased acidity as determined by phenolphthalein. From the fact that in a majority of the experiments there occurred a gradual increase in acidity (phenolphthalein) associated with no simultaneous changes in reaction to dimethylaminoazobenzene, it seems reasonable to consider that the augmented acidity was not brought about by increase in acid phosphates since dimethylaminoazobenzene would react to such change; but rather to a formation of acids of the fatty acid type to which the latter indicator is not sensitive.

In this connection emphasis must be laid upon the results of the two experiments in which ethyl butyrate was added to the autolytic mixture. The pronounced acceleration of autolysis which occurred evidently as the result of the formation of butyric acid in the mixture cannot fail to have but one significance. Given a cell in which as the result of increased lipolysis from some reason or other fatty acids are being produced in excess, their presence will markedly stimulate nitrogenous autolysis. The fat and fatty acids content of supposedly normal cells vary within very wide limits. This is a factor which must be reckoned with in the consideration of general or even nitrogenous autolysis. Whether the augumented autolysis is a result of the catalytic action of the hyrodgen ions of the butyric acid or whether the same relationship exists between the lipolytic autolyses and the decomposition of protein substances, is hard to decide.

From this somewhat cursory discussion it becomes evident that at the time when the cell becomes removed from its circulation, hydrolytic changes are set up with varying degrees of rapidity; the character of these changes is dependent upon the condition of the cell at the time. The reaction of the fluids bathing the protoplasm (if the protoplasm is considered to be neutral) is an important factor as shown by the many investigations upon the effect of acidity and alkalinity upon autolysis. The results recorded here plainly indicate however that changes in reaction which most nearly simulate those which can occur in the living cell do not alter the autolytic rate so markedly, if they do at all, as where stronger acids and alkalies are employed.

In the majority of cases only the nitrogenous autolysis has been studied. As it has been indicated, if carbohydrates are present in the cell, amylolytic autolysis will also occur; lipolytic autolysis probably is as constant as the nitrogenous process. Either one of the three types of autolysis may occur without the other. Probably all three originate when general autolysis begins. That one process influences the others and that the products of the autolytic hydrolyses (lactic acid, fatty acids, etc.) markedly influence, per haps augments the others (*e. g.*, nitrogenous autolysis) are facts rapidly being brought into prominence. Further study in this direction should lie in attempts to test the effect upon autolysis of a single type, *e. g.*, nitrogenous, by setting up simultaneously in the mixture amylolytic or lipolytic autolysis; this would also include the effect of autolytic products, upon the rate of all three types of autolysis.

CONCLUSIONS.

1. Under certain conditions, general autolysis does not begin immediately upon the removal of the organ from its circulation.

This latent period is more apt to be present in those cases in which the tissues have been temporarily cooled on account of the use of a cold saline diluent or in which the percentage concentration of the inorganic salts (calcium or potassium), of the tissues have been changed by dilution with a sodium chloride solution. The presence of blood and absence of fats and of glycogen in the cells act as important factors in prolonging the latent period.

2. Attempts to produce an alkaline reaction (phenolphthalein) in the tissue resulted negatively. Solutions of disodium hydrogen phosphate and of sodium bicarbonate when added to the liver tissues gave a mixture which was acid to phenolphthalein and no effect upon autolysis was apparent.

3. The addition of antiseptics—chloroform and toluol—markedly decreased the rate of autolysis. Ordinary light produced no effect.

4. Ethyl butyrate when added to the tissue became hydrolysed into butyric acid; the formation of this acid in the mixture caused a decided acceleration in the autolytic rate. The acidity of a solution of dihydrogen sodium phosphate failed to produce a similar result.

5. The figures for the changes in the depression of the freezing-point, non-coagulable nitrogen and reaction of the autolytic mixture do not parallel one another. In some experiments a marked increase in the depression of the freezing-point was unaccompanied by augmentation of non-coagulable nitrogen.

6. General autolysis is the sum total of proteolytic, amylolytic and lipolytic factors. Each of these autolytic factors may proceed alone for a time; the rate of one is decidedly influenced by the presence or absence of the others. The acid products which are the result of amylolytic (lactic acid) and of lipolytic (higher fatty acids) autolysis, exert a pronounced augmentative effect upon the commencement and rate of nitrogenous autolysis.

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THE INFERIOR LONGITUDINAL BUNDLE AND THE GENICULO-CALCARINE FASCICULUS. A CONTRIBUTION TO THE ANATOMY OF THE TRACT-SYSTEMS OF THE CEREBRAL HEMISPHERE.

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Ever since Burdach's time, the most external of the three sagittal layers which surround the descending and posterior horns of the lateral ventricle and which form the deep boundary of the central white matter of the temporo-occipital lobe, has been known as the inferior longitudinal bundle and considered as being composed essentially of association fibres uniting the cortex of the occipital lobe with that of the temporal lobe. More recently Sachs has proposed the term *stratum sagittale externum* for this layer of fibres and the latter denomination has gradually superseded the old one in the more modern text-books on the anatomy of the brain. But, by whatever term this mass of fibres may have been designated, the majority of observers have at all times been unanimous in regarding it as an association tract. We do not intend to analyze here the views held by the different anatomists; this being our fourth contribution to this particular chapter of nervous anatomy and an exhaustive review of the literature of the subject having figured in our original monograph[1] on the central optic or geniculo-calcarine fasciculus in 1906. We will content ourselves with recalling that Burdach's conception of the inferior longitudinal bundle has, with certain modifications of a purely anatomic order bearing upon details of morphology, relationship, etc., been shared by Arnold, Sachs, Déjerine, von

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[1] Nouvelle Iconographie de La Salpêtrière, 1906, No. 1, p. 103 and No. 2, p. 178.

Monakow, Obersteiner, Schellenberg, Edinger, Schaffer and others.

Flechsig was the first to oppose on the basis of a well-established anatomic principle, the sense of the classic doctrine regarding the physiologic character of Burdach's bundle. As the result of his researches upon the embryology of the central nervous system, more particularly with reference to the period at which the various nerve-tracts become invested with myelin, he was led to contend in 1895 that the inferior longitudinal bundle is made up exclusively of projection fibres derived from the optic thalamus (inferior segment of the lateral nucleus and main nucleus of the pulvinar) and terminating in the occipital lobe, more particularly in the visual area. After emerging from the optic thalamus, the fibres of this tract are intermingled with others having the same source and destined to the olfactory area and Ammon's horn, and with still other fibres coming from the internal geniculate body and optic thalamus and coursing to the temporal lobe and to the auditory sphere. Flechsig's doctrine soon gained hearty support and the later contributions of Probst, Niessl-Mayendorf, Redlich and others brought it abundant confirmation.

Within the last five years, a few authors (Starokolitzki, Weber) have arisen as pacificators to adjust the ominous differences between the old and the new School and have taken the very safe stand of ascribing to the inferior longitudinal bundle a mixed character, i. e., they claimed that it contains both projection and association fibres.

We were not able to view thus the constitution of the aforenamed tract and favored entirely the new doctrine which proclaims it a purely projection fibre-system. But there our task could not end, as there still remained wide differences between Flechsig's followers as regards the exact source, course, termination and physiologic significance of the total mass of fibres which go to make up the inferior longitudinal bundle.

Personally, we believe that all the constitutent fibres of the inferior longitudinal bundle are of the projection variety, but hold that this bundle represents not one but several individual tracts comprising both corticifugal and corticipetal fibres and that its constitution varies from one level to the other. Our main object has been, and still is, to isolate from the great mass of fibres which compose the inferior longitudinal bundle, a certain contingent of appreciable magnitude, and to clearly demonstrate its existence as a perfectly well-defined anatomic entity. The perfect autonomy of this fasciculus was revealed to us in the course of our researches upon the anatomy of the brain pursued in the laboratory of our teacher, Pierre Marie, at the Hospice de Bicêtre, Paris. We had occasion to systematically examine by means of serial sections eight cases of cerebral softening with involvement, to a greater or lesser extent, of the constituent fibres of the inferior longitudinal bundle. In the majority of the cases, the lesions were those characteristic of sensory aphasia (lesion of the supramarginal and angular gyri and of the bases of the first and second temporal convolutions). In one case, we had the exceptional good fortune of having to do with a strictly cortical patch of encephalomalacia extending over a considerable antero-posterior area without implication of the deep sagittal layers. Our results were constant. We found that a significant proportion of the longitudinal fibres of Burdach do not take their origin from the occipital lobe but from some anterior level, as they were always seen to degenerate caudad, i. e., behind the seat of lesion, and furthermore, that their source is not from the cortex of the temporal lobe (thus eliminating at once the possibility of their being association fibres), as these fibres were not affected by lesions limited to the cortex and subcortical substance of this lobe. In one case the entire occipital cortex and subcortex were destroyed and in the depth of the lobe one fasciculus was discernible and relatively intact, it was Burdach's inferior longitudinal bundle, which, at this level, constitutes likewise the external sagittal stratum. The only conditions under which we observed the degeneration of the inferior longitudinal bundle in the occipital lobe were: (a) the direct section of the deep sagittal layers at anterior levels, and (b) the existence of lesions of the lenticular nucleus, the external geniculate body and adjoining portion of the optic thalamus. In judging of the integrity or implication of this contingent of the inferior longitudinal bundle, it is with intent and purpose that we choose the occipital lobe as the field of decision, as we have ever and still deem it indispensable to make ourselves clear regarding the exact proportion of inferior longitudinal fibres which we wish to identify under the name of central optic or geniculo-calcarine fasciculus. Ambiguity creeps in unnoticed, and misinterpretation, while a pardonable offense, is one which is often extremely difficult to expose. We have already had to seriously contend with the pernicious effects of misquotation and are therefore anxious, even at the cost of repetition, to obviate all possibility of further misconstruction. This preliminary explanation is all the more important owing to the laxity with which the terms "inferior longitudinal bundle" and "stratum sagittale externum" are used synonymously. We have from the very outset insisted upon the fact that the term tract or fasciculus should be restricted to the designation of a bundle of nerve-fibres coursing over an appreciable distance and the territory of which remains fairly well defined throughout. The word stratum has a much wider range of application and implies little more than mere regularity of disposition of a great mass of nerve-fibres at any one point. That in the occipital lobe the distinction between these terms may have but little significance, we readily admit, but it is all otherwise in the temporal lobe, and especially in its middle portion where the retrolenticular segment of the internal capsule comes into view. At this point, indeed, the external sagittal layer contains both corticipetal and corticifugal projection fibres, it likewise harbors a certain number of association fibres. Still farther forward, the external sagittal layer is traversed by the congregating fibres of the anterior commissure, it becomes blended below the sphenoidal horn with the temporal segment of the cingulum and laterally with the innermost fibres of the fasciculus uncinatus. So that it becomes evident on all hands, that the stratum sagittale externum of Sachs varies in its constitution from one level to the other, that in the temporal lobe it differs materially from the stratum sagittale externum of the occipital lobe, and that, taken as a whole, it does not correspond to the classic description of the inferior longitudinal bundle.

What we desire to clearly establish is that the external sagittal layer of the occipital lobe, the inferior longitudinal bundle such as it exists in this lobe, is composed exclusively of projection fibres. For us, this layer represents the corticipetal complement of the occipital corona radiata; its constituent fibres take their origin from the external geniculate body and terminate in the cortex bordering upon the calcarine fissure. In order to avoid useless errors of interpretation we proposed for this contingent of projection fibres the name of "central optic" or "geniculo-calcarine fasciculus"; the latter term being more in harmony with the nomenclature recently introduced by Edinger, and which, on account of its simplicity and anatomic significance, is fully deserving of speedy and universal acceptation.

We cannot, in this connection, dwell at any length upon the facts brought out in our previous publication, regarding the true character of the inferior longitudinal bundle. We shall have abundant occasion in giving a detailed description of three additional corroborative cases of cerebral softening, to refer to many facts already signalized in our first monograph, to emphasize some and to elucidate others. But before we proceed with the actual study of these cases, it would be well perhaps to reproduce here our original conclusions regarding the inferior longitudinal fasciculus. We transcribe literally from our article in the *Nouvelle Iconographie de la Salpêtrière* (1906, No. 2, p. 215):

(1) There exists a nerve-tract, the component fibres of which occupy in the temporal lobe, partly the external, partly the internal sagittal layer, and which, in the occipital lobe, constitute almost the whole of the external sagittal layer. This tract, which represents the corticipetal corona radiata of the occipital lobe, takes its origin from the external geniculate body and terminates in both the upper and lower lips of the calcarine fissure, but more particularly in the latter. We propose for this bundle of fibres, the name of "central optic fasciculus" or better still that of "geniculo-calcarine fasciculus."

(2) This tract should be differentiated from the association fibres which constantly invade its territory. If for the sake of simplicity, usage will have it that all fibres which merely traverse a nerve-tract form part of it, we shall say that the inferior longitudinal bundle of the classic authors comprises: (a) the central optic fasciculus, and in addition (b) a certain number of association fibres.

(3) However extensive a lesion of the occipital lobe may be, a normal aspect is resumed at the level of the anterior temporal region, and we do not recognize the existence in man of the long association fibres of classic writers.

Recently, in a very interesting and instructive article, Adolf Meyer[2] brings forth additional data of unquestionable significance in demonstrating the correctness of Flechsig's view, that the external sagittal layer, or marrow, as he calls it, is constituted solely

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[2] Transactions of the Association of American physicians. Twenty-second Session, 1907, Volume XXII. Philadelphia, 1907.

by projection fibres derived from the basal ganglia and coursing for the most part to the occipital lobe, particularly to the calcarine cortex. But Meyer falls into error when he attributes to Flechsig the designation of these fibres by the term "geniculo-calcarine tract." We have already seen that this author regards the optic thalamus as the starting point of the external sagittal layer; prudent and circumspect he does not grant the entire domain of this layer to the fibres destined to the visual area, wherein he differs materially from Meyer, but includes the fibres going to the temporal lobe, more particularly to the auditory and olfactory areas. I believe that I may be credited with having introduced the term "geniculo calcarine fasciculus" and I am sure that I did not employ it as a synonym for the external saggital layer in its entirety, but for its occipital segment only. Meyer makes it a point to dwell upon a case which, in his opinion, incidentally serves to correct a claim raised by me that retrograde degeneration does not occur and that its appearance is produced by a lesion in the lenticular region. He refers to a lesion which consists of a destruction of the posterior end of the calcarine area and an undermining of the more anterior parts of the temporo-occipital base far into the fusiform gyrus, from occlusion of the posterior cerebral artery. The actual softening reaches far into the optic radiations beyond the lateral angle of the ventral segment and into the height of the dorsal segment and it destroys completely the posterior end of the lateral radiation. In keeping with this the external geniculate body is practically empty; only the most dorsal radiations are preserved as a compact bundle; the rest are almost reduced to nothing. The entire ventral portion which makes the temporal détour is degenerated. No lenticular lesion accounts for the degeneration of the geniculo-calcarine tract.

In the first place, I wish to correct in my turn the author's interpretation of my statements concerning retrograde degeneration. I have not only never maintained that it does not occur but have even related two instances in which it had been personally observed.[3] What I have tried to do was merely to point out the too great laxity with which retrograde degeneration is invoked in order to easily account for otherwise unclear degenerative pictures and the danger of doing so when discussing in-

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[3] Nouvelle Iconographie de La Salpêtrière, 1906. No. 6, p. 573. Nouvelle Iconographie de La Salpêtrière 1906, No. 2, pp. 185–188.

sufficiently established fibre-systems. In the second place, in describing one of my original cases, I attributed a zone of sclerosis situated in the inferior part of the vertical segment (frontal section) of the external sagittal layer and which could be distinctly followed throughout the temporo-occipital lobe, to a destructive lesion of the lenticular nucleus, and there is no question in my mind about the correctness of this interpretation; the sclerotic field emerges from the lower angle of a completely destroyed lenticular body, and from the inner border of this nucleus, the fibres, although atrophic, stain relatively well and can be seen to curve backward and mesially towards the external geniculate body.

I am not of those who believe that the degenerative sclerosis of a given tract must necessarily always be explained by the same factor or group of factors. Lesions vary greatly in different cases as regards both their actual extent and duration. Meyer's contention that in the first case published by him (case of idiocy with total destruction of the parietal, temporal and occipital lobes of the left hemisphere, with the exception of the posterior part of the calcarine cortex including the tip of the occipital lobe), the geniculo-calcarine tract appears in pure culture seems to me inadmissible. The voluminous stratum of fibres which figures in the three plates devoted to the illustration of this case, contains, in my opinion, other fibres besides the geniculo-calcarine; fibres destinated to the first temporal convolution and to the mesial convolutions of the temporal lobe, to the gyrus hippocampus in particular. The fact that there is no temporal cortex to receive some of them is not unmistakable evidence that all of these fibres are coursing to the calcarine cortex. In fact, the same remark could, with perfect reason, be made regarding the mesial occipital cortex; there is too little of it left to harbor the great mass of relatively healthy geniculo-calcarine fibres present, and therefore to explain the persistence of this tract *en masse*. Moreover, I do not believe it indispensable that both the beginning and the end of a tract be intact in order that it may persist, but that it will do so if its nucleus of origin is intact and the tract itself is not directly involved in the greater part of its course. If it were otherwise, we would see, in Meyer's case, a far less voluminous stratum of corticipetal fibres; being given that an appreciable portion of the calcarine area is destroyed. It is even remarkable that retrograde degeneration has not, being given that this case is one of long standing, made its appearance in this particular instance. I am of the opinion that in Meyer's most instructive case, in the same way that a large number of geniculo-calcarine fibres are preserved despite their destination to a no longer existing segment of the calcarine cortex, so exist likewise in this persisting stratum of corticipetal fibres, a certain proportion of fibres coursing to a destroyed temporal cortex. The fibres simply terminate abruptly in the peri-focal sclerotic zone without having reached their anatomo-physiologic end-station.

Let us now take up systematically the study of the three new cases of cerebral softening referred to before and which seem to us to integrally confirm our original conclusions regarding the external sagittal layer of the occipital lobe.

Case I. Tracnard. Left cerebral hemisphere. (Pl. I) Patch of softening involving the supramarginal gyrus, the base of the first temporal convolution, the whole of the angular gyrus and the adjoining portion of the second occipital convolution.

A section carried through the occipital region at a point about one centimeter behind the splenium corporis callosi shows that the lesion has extended deeply into the white matter and destroyed all the structures bordering upon the superior wall and the upper two-fifths of the lateral wall of the ventricle. On section through the splenium, it is seen that the lesion has excavated practically the whole of the supramarginal gyrus and the first temporal convolution at their point of fusion, sparing the cortex, however, so that a mere shell of cortical substance replaces the former convolutions. The process here again extends as far as the ventricular lining in the area corresponding to the upper half of the lateral wall of the ventricle, which at this point shows decided dilatation. The tapetum and sagittal layers are therefore completely destroyed in their upper segment. More anteriorly, the lesion rapidly diminishes, becoming limited to the lower border of the supramarginal gyrus and the upper border of the first temporal convolution in the depth of the Sylvian fissure. Sections passing through the hemisphere at a point one and five-tenths centimeters behind the pulvinar of the optic thalamus reveal no appreciable foci. Small patches of recent softening are also noted along the superior border of the hemisphere, involving at some points the mesial cortex, at others, the subcortex, of the paracentral lobule and base of the superior frontal convolution; but the latter lesions do not interest us as they have no bearing upon the question under consideration and cannot, moreover, lend any element of confusion.

The first section illustrating this case (Pl. I, Fig. 1) is taken from the anterior part of the occipital lobe. The lesion at this level destroys entirely the angular gyrus and the second occipital convolution at about their point of fusion, penetrating deeply and reaching almost to the stratum calcarinum which stretches over the prominence (calcar avis) caused by the dipping in of the calcarine fissure. The ventricle is prematurely closed (symphysis ventriculi). The Gennari streak can be seen with unusual distinctness. The softening has destroyed the tapetum, the internal and external sagittal layers, corresponding to the dorsal or upper half of what may be termed the lateral segment of these structures. It will be seen that owing to the closure of the occipital horn, the deep layers have practically but a vertical extent and that they are divisible into a mesial and a lateral segment, between which the tapetum intervenes. In the lower part of the section and going outward from the bottom of the calcarine fissure, we can distinguish several layers regularly disposed: (1) a broad band completely degenerated which represents the tapetum, (2) the internal sagittal. layer or inner optic radiation of Flechsig, derived from the occipital cortex and coursing to the pulvinar of the optic thalamus. It is moderately and diffusely degenerated, owing, in part, to the presence of fibres derived from the lateral convolutions of the occipital pole which are themselves undermined by the softening, and, in part, to its close proximity to the lesion at this level. (3) The external sagittal layer, which in this region is constituted essentially by the geniculo-calcarine tract. The ventral segment of this tract is practically normal, as it has not been involved at any point in its course through the more frontal regions. (4) Closely investing the geniculo-calcarine fasciculus externally and almost blended with it, a narrow band may be seen on close inspection; it is distinctly degenerated and may be followed with the external sagittal layer into the depth of the lingual lobule. This outermost layer contains association fibres derived from the lateral convexity and coursing to the lingual lobule. It is thus made up of fibres which form part of the association bundles known as Wernicke's perpendicular occipital fasciculus and Vialet's transverse fasciculus of the lingual lobule. From the regularity of its disposition one would almost be tempted to describe a *stratum sagittale extremum occipitale.* It is not the first time that I see the deep association fibres of the occipital lobe assume this layer-like disposition, and this fact amply suffices, in my opinion, to explain the many difficulties encountered by the earlier writers in their attempts to define the character of the external sagittal layer. It shows once more the perplexingly intimate relationship between projection and association fibres.

Von Monakow illustrates in his work[4] the occipital degeneration in a case of cortical hemianopsia. The lesion, situated in the interparietal fissure, almost completely destroys the upper segment of the angular gyrus and the contiguous portion of the superior parietal convolution, dipping down to the ventricular ependyma of the superior wall of the occipital horn. The drawing shows a degeneration of the entire external sagittal layer (which the author calls the inferior longitudinal bundle), so that a degenerated ring practically encircles the ventricular horn. The degenerated fibres must therefore pursue a vertical course and can only

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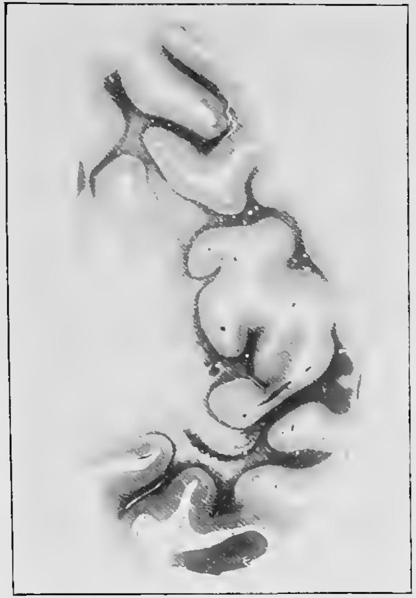
[4] Von Monakow-Gehirnpathologie p. 752. Taken from Nothnagel's Specielle Pathologie u. Therapie, IX Band, Wien 1905.

PLATE I



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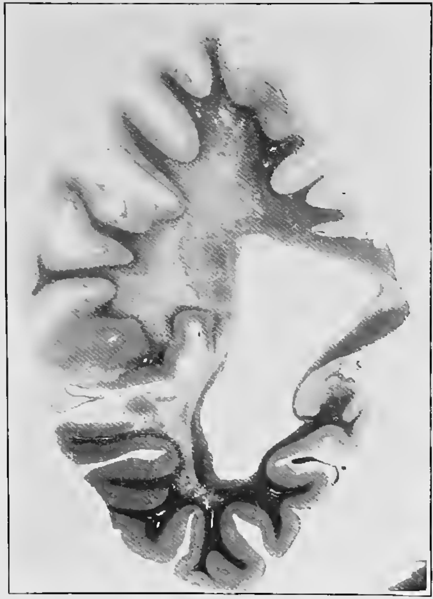

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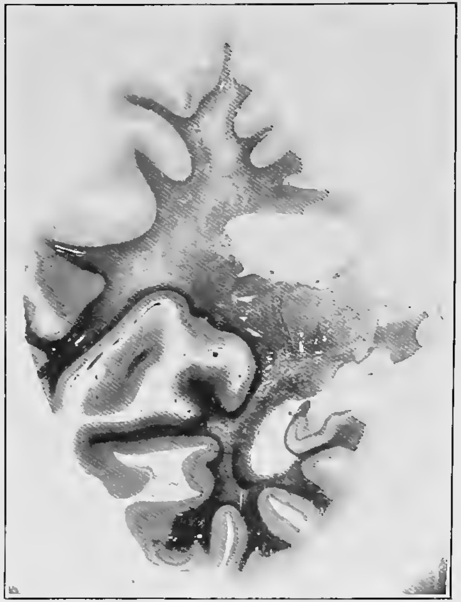

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represent the association fibres of the region. We know indeed from the direction of the constituent fibres of the external sagittal layer, that it is impossible for a lesion limited to the superior convolutions of the parieto-occipital convexity to determine a secondary degeneration of the total mass of its fibres. It can only react upon the fibres of its dorsal segment. It thus becomes evident that in von Monakow's case, the degenerated fibres do not form part of the external sagittal layer, properly speaking, but that they simply closely invest it externally; a conclusion, moreover, which one would readily deduce from a careful study of the drawing. It is well to recall, in this connection, that von Monakow is among those who regard the external sagittal layer as an association tract, and it may further be stated, that the same author does not recognize the existence of Wernicke's vertical occipital fasciculus. This combination of factors largely suffices to explain von Monakow's interpretation of the degenerative picture in his case. It seems to me, however, that he has by this very instance furnished a most convincing demonstration of the existence of Wernicke's bundle. It is because von Monakow's case closely resembles ours, particularly with regard to the occasional development of an extreme sagittal layer of association fibres, that we have thought it useful to insert right here this extrinsic discussion.

The next section (Pl. I, Fig. 2) is one through the anterior part of the splenium of the corpus callosum, near the point where it lodges anteriorly the body of the fornix. The splenium shows a very considerable degeneration of its central portion. The descending horn of the lateral ventricle is appreciably dilated. The lesion has already retroceded in great part and is now confined to the edges of the Sylvian fissure, destroying the superior border of the first temporal convolution in the depth of the fissure, and the outermost segment of the inferior border of the supramarginal gyrus. Very small foci of softening may be seen in the subcortex of the paracentral lobule. There is no longer any actual implication of the deep sagittal layers. The tapetum is very thin and greatly degenerated along the lateral ventricular wall. The corona radiata of the parietal lobe is easily distinguishable, and microscopically, it may be seen to send many fibres to, or else receive the same from, the paracentral lobule. Corresponding to the temporal lobe, three strata can be differentiated outside the ventricular wall: the tapetum, the internal and the external sagittal layers. A point especially worthy of consideration, and one upon which I have previously laid much stress is, that opposite the deep substance of the first temporal convolution, there occurs a gradual transposition of the constituent fibres of both sagittal layers; that is to say, the fibres of the external sagittal stratum are pressed inward towards the ventricular wall and crowded against the lower pole and lateral border of the sphenoidal prolongation of the caudate nucleus, while the fibres of the internal sagittal layer pass outward and above the former, occupying both the external and internal sagittal layers. This interchange of domain is a slow but steadily progressive one, beginning posteriorly at a point which corresponds approximately to the termination of the fissure of Sylvius, and continuing as far forward as the level of the pulvinar of the optic thalamus. There is no section in my possession which illustrates this point as clearly as that actually under consideration. We note, between the ventricular wall and the bottom of the Sylvian fissure, a broad zone of degeneration which occupies, above, the territory of both the external and internal sagittal layers; it then extends obliquely downward and outward, encroaching less and less upon the internal and occupying more and more the external sagittal layer, until it reaches a point opposite the parallel fissure, where it is seen to cross obliquely the thickness of the external sagittal layer, normal at this point, and to wend its way towards the internal layer. Bearing in mind the extent of the lesion in the occipital lobe, it is evident that this broad degenerated band contains, before all, the thalamic radiations which have been intercepted in their course from the calcarine and other areas of the occipital cortex to the optic thalamus. Only a small proportion of geniculo-calcarine fibres have been severed, and even retrograde degeneration could not account for the marked degenerative sclerosis observed at this point in the external sagittal layer. Moreover, it must be stated that the case is not one of long standing, and not one, therefore, likely to determine a very appreciable degree of retrograde degeneration. Furthermore, as we shall see later, this degenerated area disappears about the pulvinar and dorsal nucleus of the optic thalamus, the anterior corpus quadrigeminum and the internal geniculate body. No appreciable degeneration can be followed to the external geniculate body, nor is this nucleus the seat of any atrophy. I have always maintained that the external sagittal layer of the temporal lobe differs materially from that of the occipital lobe, and that it is erroneous to look upon the external sagittal layer throughout, as a structure of unvarying character, as an anatomo-physiologic entity. This section clearly demonstrates that in the temporal lobe the external sagittal layer contains something else besides the geniculo-calcarine fibres. We have just seen that it harbors the migrating occipital radiations; in addition, it receives fibres derived from the first temporal convolution and coursing to the optic thalamus and internal geniculate body. I believe that it likewise contains fibres which take their origin from the basal ganglia and go to the mesial cortex of the temporal lobe, more particularly to the gyrus hippocampus. The very particular transposition which takes place between the thalamic radiations and the fibres of the external sagittal layer appears to me to be a most logical process; as they approach their end nuclei (pulvinar and anterior corpus quadrigeminum), these cortical radiations take the shortest route and assume the disposition which will ensure free irradiation into them, crowding back temporarily, so to speak, the other fibres whose connections are situated at more anterior levels.

The following section (Pl. I, Fig. 3) passes through the most posterior portion of the superior frontal convolution, the ascending frontal and parietal convolutions, the middle portion of the temporal lobe, the anterior corpus quadrigeminum, the optic thalamus, the internal geniculate body, the posterior capsule of the external geniculate body, the retrolenticular segment of the internal capsule and the body and sphenoidal horn of the lateral ventricle. Small patches of encephalomalacia are again observed in the cortex and subcortex of the superior border of the hemisphere, involving the base of the superior frontal convolution and having determined an appreciable pallor of the corona radiata and of the deep substance of the supra-Sylvian convolution (projection and association fibres). At this level, the temporal lobe appears normal save for the presence of areas of degeneration. The deep substance of the first temporal convolution is appreciably degenerated owing to the interruption, in more posteriorly situated regions, of the association fibres which terminate in its cortex. The lower part of the retrolenticular segment and the sublenticular segment of the internal capsule show a very decided degree of degenerative sclerosis. It is seen that this degenerated area forks when it reaches Wernicke's field, one division containing the radiations of the destroyed parietal convolutions continuing upward outside the lamina medullaris externa of the optic thalamus to terminate in the dorsal nucleus of this body; the other containing the radiations of the first temporal convolution passing horizontally inward through the superior portion of Wernicke's field, above and behind the external geniculate body, to finally irradiate into the substance of the internal geniculate body, which shows a very appreciable degree of discoloration and atrophy. Likewise to be noted, is the discoloration more particularly of the middle layer of the anterior corpus quadrigeminum, resulting from involvement of the radiations derived from the visual area.

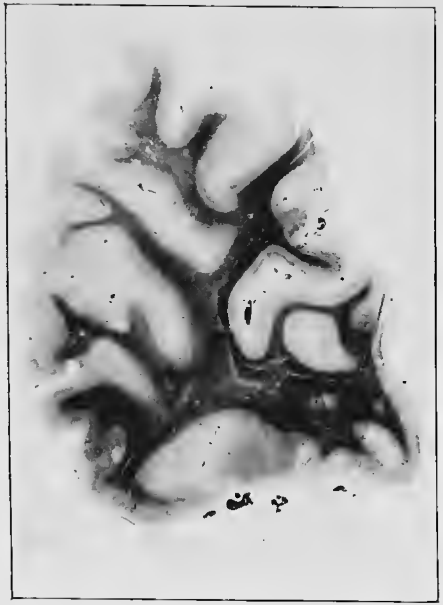
Case II. Can.... (Pl. II and III).

Extensive patch of softening from obliteration of the left Sylvian artery. The lesion, one of long standing, destroys the deep substance of the Sylvian border of the base of the ascending parietal convolution, the inferior gyri of the island of Reil, practically the whole of the supramarginal gyrus, the most anterior portion of the angular gyrus, the greater part of the first temporal convolution and its accessory superior Sylvian lobule (*circonvolution temporale profonde* of Déjerine) and the deep substance of the posterior two-thirds of the second temporal convolution. A small focus of softening is also found in the deep substance of the anterior extremity of the gyrus hippocampus. A section taken at the level of the descending horn of the lateral ventricle (Pl. II, Fig. 3) shows that the lesion has peculiarly respected, in great part, the cortex, but widely destroyed the white matter, dipping down at several points practically to the lateral ventricular wall and severing along almost its entire vertical extent the deep sagittal layers, save at the infero-external angle. Corresponding to the middle portion of the ventricular wall, it will be seen that although the softening does not extend as deeply at this point, there remains but a sclerotic area absolutely devoid of medullated fibres, as this very territory is itself involved at slightly posterior levels.

The first section (Pl. II, Fig. 1) is taken from the posterior part of the occipital lobe. This lobe, it will be remembered, is absolutely free from lesion. At once it is seen that the degenerative sclerosis is strictly confined to the domain of the external sagittal layer. Close inspection will show that it forms practically a complete ring, although evidently very irregular in contour, having somewhat the shape of the letter L, enclosing the tapetum and optic radiation which at this point are normal. The section passes immediately behind the tip of the occipital horn, which in this case is prematurely closed, so that the apposed ventricular walls simply form a vertical septum upon which border, on either side, the tapetum, the internal and external sagittal layers. The tapetum in the actual section may be recognized as a deeply-staining line extending vertically through the middle of the area marked out by the degenerated band. On either side of it a broader and less deeply-stained layer can be made out which represents the optic radiation of cortical derivation; it is especially distinct along the lateral margin of the vertical segment and in the short transverse inferior segment of the field under consideration. The external sagittal layer is so sharply isolated as the result of secondary degeneration that it would seem to have been traced with the point of a pin. It is constituted essentially by the fibres of the geniculo-calcarine fasciculus, which at more anterior levels have been practically totally wiped out by the softening above described. This section shows that in the occipital lobe, these fibres are much more abundant in the ventral segment of the external sagittal layer than in its dorsal segment, which can be seen to consist of a mere line, describing a sort of conic figure as it caps over the tapetum and then descends along its mesial aspect and just without the stratum calcarinum previous to its irradiation into the cortex of the cuneate lip of the calcarine fissure. I have had occasion several times to observe a massive degeneration of either the ventral or dorsal segment of the occipital external sagittal layer, but this is the first time that I see this layer degenerated in its entirety in an otherwise perfectly healthy occipital lobe.

The following section (Pl. II, Fig. 2) passes through a more anterior part of the occipital lobe. Symphysis of the occipital horn here again obtains, but the formation of the forceps major of the corpus callosum lodged in the deep substance of the cuneus is plainly visible. Its continuation inferiorly as the tapetum is still to be distinguished owing to its deeply-staining reaction, and appears as a dark line extending at first vertically downward, then curving mesially beneath the bottom of the calcarine fissure and penetrating into the depth of the lingual lobule. To its outer side, and within the outermost completely degenerated band, the internal sagittal layer of cortical radiations can be made out; it is diffusely degenerated owing to the influence of retrograde changes as we are nearing the seat of lesion. Finally, we observe again the extreme sclerosis of the external sagittal layer (geniculo-calcarine fasciculus), which is almost as sharply defined as in the preceding section. Yet, it is to be noted, that both the superior and inferior transverse segments of this sclerotic band are not strictly confined to the domain of the external layer. Above, the degenerated fibres are seen to closely invest the forceps major, passing therefore through the internal sagittal layer; below, the broad degenerated band of geniculo-calcarine fibres destined to the lingual lobule is interrupted, so to speak, at two points, by normal fasciculi. The more lateral one contains but a small number of fibres and truly belongs to the geniculo-calcarine tract; it has simply escaped involvement in its long course through a partly softened, partly sclerotic

PLATE II



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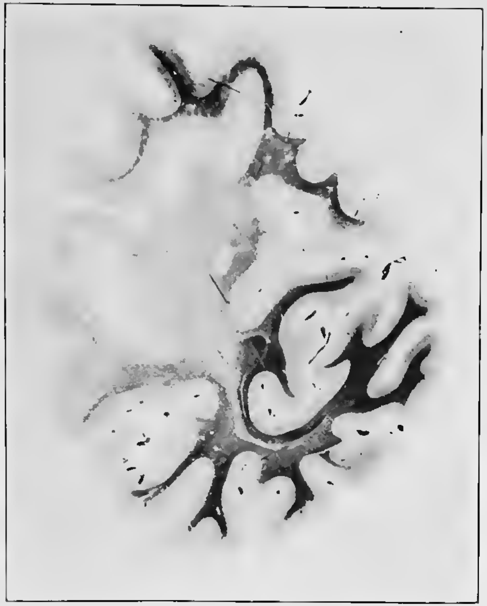

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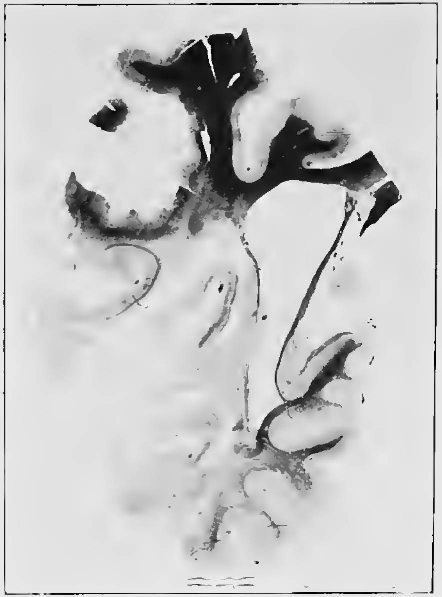

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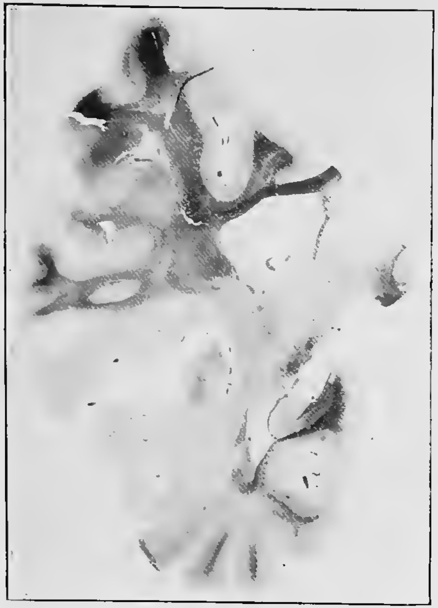
territory. The more mesially situated healthy fasciculus is much more considerable and does not belong to the geniculo-calcarine tract, but is formed of cortical optic radiations. Careful study will show, indeed, that to the inner side of the lateral normal fasciculus, the degenerated line no longer follows the external layer, but sinks into the internal layer close to lingual segment of the tapetum, and through this channel irradiates into the lower lip of the calcarine fissure, the deep substance of which may be seen to be appreciably degenerated in consequence. So that, if it may be said that the lateral or vertical segment of the occipital external sagittal layer is constituted essentially by corticipetal fibres, or more accurately, by the geniculo-calcarine fibres, differing thus very materially from the corresponding segment of the internal sagittal layer which contains before all corticifugal fibres, or the thalamic radiations of the occipital cortex, the same differentiation cannot be made with regard to the dorsal and ventral mesially-directed segments of these layers. The fibres of the geniculo-calcarine tract situated at both the superior and inferior angles of the lateral segment of the external sagittal layer, in order to reach their field of irradiation, i. e., the cortex bordering upon the calcarine fissure, naturally follow the shortest course which is via the internal sagittal layer. They necessarily mingle with the optic radiations and even crowd the latter aside on arriving close to their point of arborization, so that in the depth of the cuneate and lingual lobules, the internal layer is occupied more particularly by the terminating than by the originating fibres. This feature, moreover, is the rule throughout the cerebro-spinal axis. We have already seen a similar disposition at the level of the optic pulvinar between the terminating thalamic radiations and the emerging geniculo-calcarine fibres.

The pallor of the deep substance of the lateral convolutions, more particularly of the angular gyrus and second occipital convolution, is due, in great part, to the interruption at slightly anterior levels of a large number of association fibres. The peculiar cribriform appearance of the subcortex of the second occipital convolution is a common finding, in my experience, in regions which are themselves intact but which have been long deprived of their afferent medullated fibre-systems. Microscopically, Wernicke's vertical occipital bundle is clearly demonstrable opposite the second and third occipital convolutions, and the same may be said of Sachs's *fasciculus proprius cunei* which is plainly appreciable even in this figure; the mesially-directed dorsal segment of the degenerated geniculo-calcarine tract separating it from the forceps major of the corpus callosum.

The next section (Pl. II, Fig. 3) has already been considered in the general description of the lesion of this case. There is complete destruction of the supramarginal gyrus and first temporal convolution and extensive undermining of the second temporal convolution. At the infero-external angle of the ventricle, the deep sagittal layers can be plainly recognized and ascend for a very short distance along the lateral ventricular wall, terminating above in a field, which, although bordering directly upon a cavitary focus, contains a fair number of well-stained fibres which have peculiarly escaped destruction. This island of healthy fibres belongs, in great part, to the geniculo-calcarine tract and is identical with the normal lateral fasciculus described in the preceding section in connection with the external sagittal layer. Below this field, the sagittal layers are totally degenerated and seem continuous with the equally totally degenerated subventricular segment of the internal sagittal layer. Microscopically, it is seen that this sclerosis extends mesially into the depth of the gyrus hippocampus; so that it may be safely assumed that at this level, the external sagittal layer contains a certain number of fibres which go to the mesial convolutions of the temporal lobe *via* the subventricular segment of the internal sagittal layer. The corresponding segment of the external sagittal layer is relatively normal and well-developed; we are of the opinion that in this region there enters into its formation, aside from the geniculo-calcarine tract, a large number of fibres derived from the mesial convolutions, more particularly from the gyrus hippocampus. A certain proportion of these may perhaps follow an inverse course, going to the same region from the basal ganglia.

A section taken at the level of the pulvinar of the optic thalamus (Pl. III, Fig. 4) shows the extreme discoloration and atrophy of this body, resulting from interruption of the great majority of the occipital radiations. The anterior corpus quadrigeminum being connected with the thalamus at this point, it is readily seen that the secondary degenerative sclerosis traverses the entire breadth of the pulvinar passing directly into the superficial and middle zones of the colliculus, and that it may even be followed into the quadrigeminal commissure as far as the mesial line. The only region of the pulvinar which contains normal-staining fibres is that situated at its infero-external angle; it corresponds to the external retro-geniculate area and forms the lower part of what is classically known as the triangular field of Wernicke. The fibres which constitute this normal area take their origin, for the most part, from the external geniculate body. The remaining mesial segment of the lower border corresponds to the internal retro-geniculate field; it is exceptionally degenerated and shrunken as it receives the cortical radiations of the first temporal convolution, which, as we have already seen, is destroyed in the greater part of its extent. The lesion at this point involves the Sylvian border of the ascending parietal convolution, spares the contiguous portion of the island of Reil but undermines its temporal portion, completely destroys the first temporal convolution and sinks into the deep substance of the second temporal, whence it extends more deeply at one point and completely severs the external and internal sagittal layers. The latter focus exactly replaces in this section the sclerotic field observed in the previous section at the infero-external angle of the sphenoidal horn. The normal fibres which then lay immediately above it are now seen to trend mesially towards the lower pole and lateral border of the sphenoidal prolongation of the caudate nucleus. These fibres, it will be remembered, we attribute to the geniculo-calcarine fasciculus. Below the seat of lesion, the external sagittal layer appears diffusely degenerated owing to the presence, at more anterior levels, of additional linear extensions from the main area of softening. The tapetum and internal sagittal layer are likewise appreciably degenerated. The intense degeneration of the retro-

PLATE III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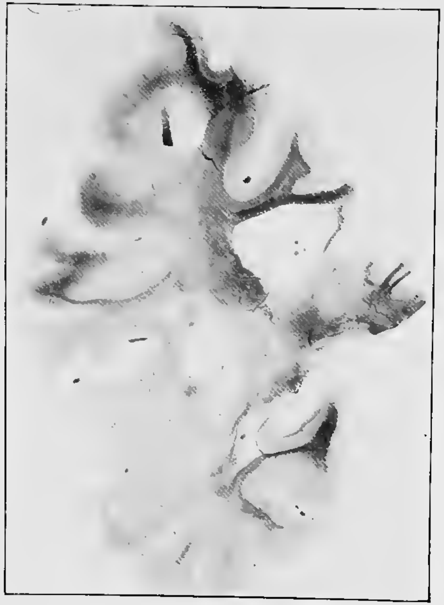
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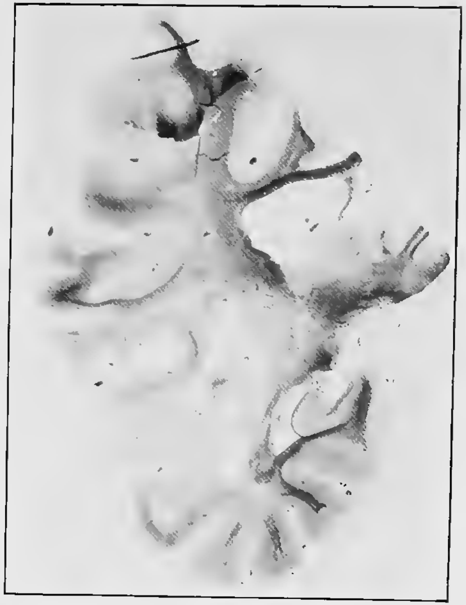
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and sublenticular segments of the internal capsule is fully explained by the interruption of all the cortical radiations derived from the occipital lobe, the first and second temporal convolutions, the insular region and the supra-Sylvian gyri. Retrograde degeneration of the internal and external geniculate fibres undoubtedly contributes its share towards rendering this sclerosis so extreme. Without the sagittal layers, the marked discoloration of the deep substance of uninvolved convolutions reveals the widespread connections of the association fibre-systems, the interdependence of supposedly distinct association tracts. In the temporal lobe, the pallor of the subcortex extends beneath the sphenoidal horn into the depth of the gyrus hippocampus, thus showing that the inferior segment of the cingulum reacts to lesions of the lateral convexity. This involvement of the cingulum serves at the same time to delimit the subventricular segment of the external sagittal layer, a projection-path with which it is so intimately blended in the normal state that it is impossible to distinguish between them. This very intimacy of relationship has unquestionably been a most potent factor in inducing the earlier writers to regard the ventral portion of the external sagittal layer as an association bundle. In the parietal lobe, likewise, the degeneration of the fasciculus arcuatus extends high up into the ascending frontal convolution, sharply defining the base of the corona radiata against the short subcortical association-loops. The degeneration even affects the fronto-parietal or superior segment of the cingulum, and despite the unfortunate tear in the upper part of the section, the pallor of the deep substance of the gyrus fornicatus is distinctly appreciable. There exists a considerable atrophy of the body of the corpus callosum and of the fornix. A last feature of interest is the sharpness of outline of the anterior and posterior brachia of the quadrigeminal bodies resulting from the extreme discoloration of the superficial and middle layers of the anterior colliculus.

The following section (Pl. III, Fig. 5) passes through the most posterior portion of the external geniculate body which is seen to be decidedly atrophied, shrunken and discolored, especially in its mesial segment, as the result partly of retrograde degeneration and partly of prolonged functional inactivity. Nevertheless, the lateral limiting field of Wernicke is abundantly supplied with healthy nerve-fibres except in its superior portion, where it is traversed by the dorsal fasciculi of the geniculo-calcarine tract in their course from the geniculate body to the vertical segment of the external sagittal layer. That these bundles have undergone retrograde degeneration, there can be no doubt. Their course through the retrolenticular segment of the internal capsule is easily followed. Immediately beneath this degenerated zone, several obliquely-directed healthy fasciculi are seen to abandon the external sagittal layer and to wend their way mesially and upward towards Wernicke's field; they are the very fibres which, in the preceding section, were seen to collect about the caudate nucleus. They have simply been displaced upwards in their forward course and pass gradually into the lowermost field of the internal capsule. Similarly, it will be noticed that the next lower segment of the external sagittal layer, previously occupied by a focus of softening, now a thoroughly sclerotic area, tapers down to a fine filiform process as it passes upward and inserts itself between the caudate nucleus and the overlying healthy fasciculi, which it thus displaces upward and laterally towards the external capsule and into the retrolenticular division of the internal capsule. This section, I consider admirably suited, owing to this rare alternation of preserved and degenerated fasciculi of geniculo-calcarine fibres, to demonstrate the peculiar détours which these fibres follow in reaching the external sagittal layer after their emergence from the external geniculate body. All these features were incorporated, however, in my first description of the geniculo-calcarine tract. A fact to be noted, is that the healthy fasciculi coursing towards Wernicke's field comprise a larger number of fibres than the sum total of the fibres which escaped involvement and which form the normal field observed at the infero-external angle of the sphenoidal horn. This reappearance of normal-staining medullated fibres in the domain of the retro- and sublenticular segments of the internal capsule steadily increases as we consider more and more anterior levels, and this fact, coupled with the existence of a fairly well-supplied field of Wernicke, clearly shows that there is a partial restoration of the degenerated geniculo-calcarine tract before it reaches its nucleus of origin, the external geniculate body. In other words, ascending, cellulipetal or retrograde degeneration has not extended over the entire length of the central segment of the divided nerve, but has become arrested at a variable distance from its trophic centre. The linear degeneration of the remainder of the external sagittal layer has become more distinct. The degeneration of the internal sagittal layer is well-marked and involves more particularly the constituent fibres of Türck's fasciculus, of which that layer at this level is largely composed. The retrolenticular segment of the internal capsule is less widely degenerated than in the preceding section but the sclerosis is more intense. The fronto-parietal corona radiata which was previously relatively well-preserved, now presents an appreciable degeneration more especially of its lateral field (*stratum sagittale externum fronto-parietale* of Anton and Zingerle); its mesial division, on the contrary, remains practically normal. This latter segment of the fronto-parietal corona radiata has received several names: "corona radiata of the caudate nucleus" (Meynert); "callosal fasciculus coursing to the internal capsule" (Wernicke, Gratiolet, Foville); "reticular zone of the corona radiata" (Sachs); "stratum sagittale internum" (Anton and Zingerle). This last designation appears to us to be the most appropriate for this layer which contains fibres belonging to both projection and commissural systems. The commissural fibres are fewer in number, pursue a vertical course (on a frontal section) and simply represent the callosal radiations going to and from the island of Reil and the first temporal convolution; so that the predominating and therefore distinctive element of the fronto-parietal internal sagittal layer is the projection-fibre. Sachs has always maintained this view and demonstrative cases have been published by Anton-Zingerle[5] and by me[6]. It is

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[5] Anton Zingerle: Bau, Leistung und Erkrankung des menschlichen Stirnhirnes, pp 155–160, Graz 1902.

[6] Nouvelle Iconographie de La Salpêtrière, 1906, No. 2, pp. 200–201.

this very structure, it will be remembered, which Déjerine and others have attempted to isolate as a long association tract "the occipito-frontal fasciculus." If such were the true nature of the internal layer of the fronto-parietal corona radiata, I should certainly expect to find it appreciably compromised in this case in which there is complete destruction of the deep sagittal layers bordering upon the lateral wall of the descending horn of the lateral ventricle and interruption therefore of the great majority of the fibres of occipital derivation. On the contrary, we find it remarkably intact. It remains so throughout the series of sections, despite the fact that for some considerable distance anterior to the actual level, the supra-Sylvian convolution continues to be the seat of lesions which encroach upon the proximal field of the corona radiata and which have determined a marked degeneration of the entire posterior limb of the internal capsule. It thus becomes evident that the internal sagittal layer differs materially from the external layer as regards the source and connections of its constituent fibres. I have already expressed the opinion that this layer is in relation with the mesial surface of the fronto-parietal lobe, more particularly with the gyrus fornicatus, and that its fibres are mainly corticipetal, taking their origin probably from the anterior tubercle and mesial nucleus of the optic thalamus. There is an appreciable discoloration and atrophy of the dorsal half of the optic thalamus, most marked in the region of the lateral nucleus which is in relation with the parietal lobe. The mesial segment of the thalamus is likewise rather pallid, but it is normally poor in medullated nerve-fibres. Lying directly upon its ventricular surface is seen the ganglion habenulae with its ascending fasciculus, the taenia thalami. The posterior commissure appears very distinctly subdivided into two bundles, of which the superior represents the stem of the pineal gland. The internal geniculate body is markedly atrophic and flattened from above downward; its ventral segment is totally empty, whereas its dorsal segment receives the terminating fibres of the posterior brachium which may also be followed microscopically into the dorsal laminae of the external geniculate body. The degeneration of the parietal and temporal divisions of the cingulum is still distinctly appreciable.

The next section (Pl. III, Fig. 6) differs but very little from the foregoing from which it is separated by only three serial numbers. It is mainly intended to show the appearance of the external geniculate body at the level of its full development. It will be seen that this body has preserved its gross morphology, but that it is decidedly atrophic generally and that its transverse diameter particularly is much reduced. On closer study, it appears, so to speak, bisected in its vertical extent; its mesial segment, totally discolored, is more slender, shorter and does not appose itself fully to the outer segment, but seems displaced upwards. The lateral segment presents the typical laminated arrangement and is limited externally by the triangular field of Wernicke which is rapidly gaining in number of medullated nerve-fibres. The sublenticular division of the internal capsule is likewise more abundantly supplied. The aspect of the external geniculate body is typical and there can be no doubt that in the production of this marked discoloration and atrophy, retrograde degeneration has been chiefly concerned; but it must not be forgotten that the softening is one of old date and that the geniculo-calcarine tract has been intercepted at a relatively proximal distance from its nucleus of origin, much nearer the external geniculate body than the calcarine cortex. We have thus present the two main elements which determine retrograde degeneration, chronicity and proximity of lesion. This appearance is rare, I believe, in lesions even of long standing limited to the occipital lobe. I have often seen under such circumstances, a generalized atrophy of the external geniculate body but without appreciable concomitant discoloration; the proximal portion of the geniculo-calcarine tract would be reconstituted in front of the lesion though it would likewise present a distinct atrophy. The atrophy of both the geniculate body and its tract, I attribute to the unquestionable influence of functional inactivity.

Case III. Col.... (Pl. IV,).

Central softening of the right temporal lobe from obliteration of the sphenoid branch of the middle cerebral artery. The lesion, one of only four weeks' standing, extends from the tip of the temporal pole in front to about the level of the anterior border of the splenium of the corpus callosum behind. The patch is irregularly pyramidal in shape, with its base directed forward and its apex inserted in the tapetum of the descending horn of the lateral ventricle below the point where the caudate nucleus curves forward to pass into the sphenoidal horn. The lesion spares at all points the cortex and the immediate subcortical zone. Anteriorly, at the level of the anterior border of the external geniculate body (Fig. 1), the softening destroys all the deep white matter situated to the outer side of the sphenoidal horn, i. e., the deep substance of the three temporal convolutions and the fusiform lobule; it spares entirely the gyrus hippocampus. It is limited above by the lenticular nucleus which is itself totally undisturbed, internally by the ventricular wall, below and to the outer side by the subcortex of the temporal convolutions. The destruction has been so extreme that a cavity with jagged walls is all that remains of the centrum of this region. The occipital lobe is absolutely intact.

This case, like the others, has been studied by means of serial sections from the temporal to the occipital pole. The temporo-parietal sections have been stained according to the Weigert-Pal method; the entire occipital lobe has been subjected to osmic acid impregnation.

A section taken at the level of the full development of the external geniculate body (Pl. IV, Fig. 1) shows that all that remains of the white matter of the temporal lobe is the subcortical system of short association fibres. These fibres stain relatively well and the Baillarger streak is noticeably well-preserved in the cortex of the first temporal convolution. The external geniculate body has retained its normal configuration but appears atrophic, it is shrivelled up generally and flattened from side to side; its myelin-lamellae though well-stained are pressed closer together and present numerous angular deflections. At more posterior levels, the inner segment of the external geniculate body is not only atrophied but even discolored and no longer apposes itself fully to the outer segment, thus producing the peculiar bisected appearance already observed in the preceding case. Nevertheless, in this as in all other sections passing through the external geniculate body, it is seen that Wernicke's field is unusually well-supplied with normal-staining medullated fibres. From the upper part of Wernicke's field a considerable number of them can be followed outward into the peri-focal sclerotic zone; they represent, for the most part, geniculo-calcarine fibres which have not yet undergone retrograde degeneration. The lower part of Wernicke's field, however, is occupied by several decidedly degenerated fasciculi which belong to Arnold's temporo-thalamic bundle, the fibres of which course from the temporal pole to the optic pulvinar. At slightly anterior levels, a fairly broad and totally sclerosed fasciculus can be followed from the sublenticular segment of the internal capsule, above the external geniculate body and the optic tract, into the outermost division of the pes pedunculi; it represents Türck's temporo-cerebellar tract. In the actual section the lower field of the posterior limb of the internal capsule is diffusely but distinctly degenerated. The external and extreme capsules are markedly degenerated and the discoloration may be followed upward into the subcortex of the parietal convolutions as high as the superior hemispheral border. Beneath the sphenoidal horn, the transverse segment of the external sagittal layer is partly preserved, but it consists at this level especially of the fibres of the cingulum and its relative integrity may be explained by the fact that the gyrus hippocampus is intact. Below this layer the subcortex is decidedly discolored and the degeneration extends very distinctly into the most mesial portion of the gyrus hippocampus where it occupies the domain of the cingulum. The corresponding portion of the tapetum contains a few deeply-stained fasciculi which seem to emerge from the hippocampal septum and which advance beyond the infero-external ventricular angle.

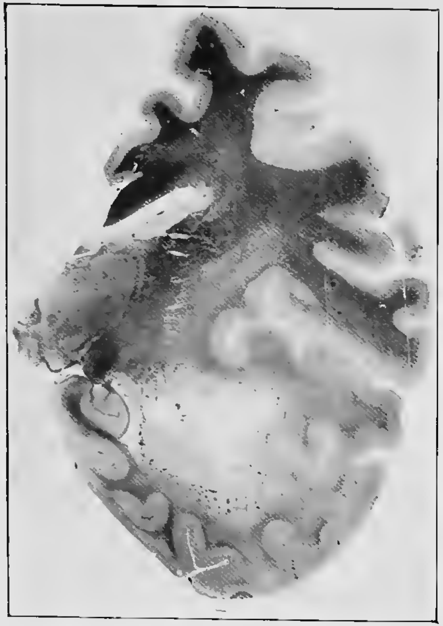
The internal sagittal layer of the fronto-parietal corona radiata is practically intact and in this particular series of sections appears unusually well-defined. It will be noticed, however, that the adjacent subependymal zone is distinctly degenerated, and that the discoloration extends into the hook-shaped peri-ventricular portion of the corpus callosum and then mesially along the lower border of the callosal commissure; showing that anterior temporal lesions react upon the trunk of the corpus callosum. An appreciable degeneration is observed in the mass of fibres (dorsal thalamic bundle) which course along the superior border of the optic thalamus and join the contiguous portion of the internal capsule. The area of degeneration extends downward outside the lamina medullaris externa of the optic thalamus and is probably related to the lesion of the fibres derived from the hippocampal and uncinate gyri. I have previously referred to the fact that important connections are established between the optic thalamus and the gyrus fornicatus, or first limbic convolution, through the dorsal thalamic bundle and the internal sagittal layer of the fronto-parietal corona radiata; it is possible that this bundle serves to establish similar connections with the gyrus hippocampus, or second limbic convolution, by means of fibres which traverse the temporal corona radiata and the internal capsule. A very distinct pallor is noticeable in the domain of the internal geniculate body and in the deep portion of the anterior corpus quadrigeminum.

The sections intervening between this one and that next to be described show a very decided atrophy and discoloration of the mesial segment of the optic thalamus which we know to be in relation with the temporal convolutions. The area of softening becomes more and more circumscribed, abandons the subcortex of the first temporal convolution and recedes from the lower hemispheral border, forming a quadrangular focus limited to the deep sagittal layers which border upon the lateral ventricular wall. The posterior and retrolenticular segments of the internal capsule appear diffusely degenerated throughout the series of sections, and this degeneration, which is too widely distributed to correspond exclusively to the passage of the temporal cortical radiations into the optic thalamus, evidently represents in part the temporal fibres which reach the corpus callosum via the external and internal capsules.

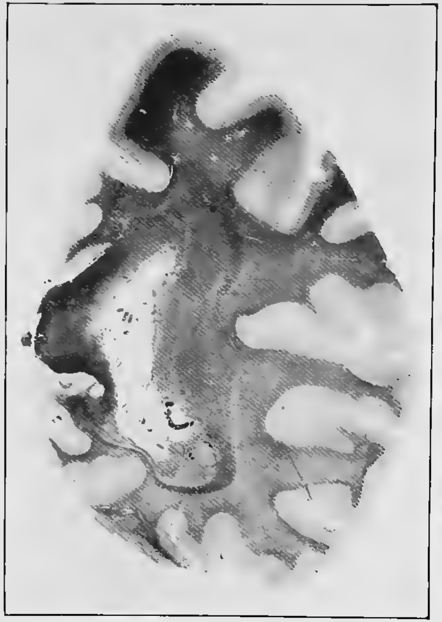
A section passing through the splenium of the corpus callosum (Pl. IV, Fig. 2) shows that the lesion is now confined to that portion of the tapetum and internal sagittal layer situated immediately beneath the descending segment of the caudate nucleus. A distinct degeneration is observed in the central portion of the splenium and extends upward along the lower segment of the forceps major. The internal sagittal layer of the parietal corona radiata is still readily discernible and apparently normal. In the temporal lobe, the external sagittal layer has become reconstituted practically in its entirety, whereas the internal sagittal layer is massively degenerated, appearing as an exceptionally well-defined sclerotic band which courses mesially below the sphenoidal horn and disappears in the depth of the gyrus hippocampus where it blends with the area of degeneration of the cingulum. The ventral portion of the tapetum like the external sagittal layer is in good part restored, but peculiarly enough, both these structures are far less preserved than would appear from the macroscope study of this section and from comparison with the markedly discolored internal sagittal layer. Microscopically, it is seen that the external sagittal layer, its ventral segment more particularly, contains but few normal fibres. For the most part, the fibres are coarsely fragmented or reduced to irregularly beaded shreds, and the whole layer is stuffed with granular bodies. That such an altered fibre-mass should still exhibit relatively good staining qualities would seem at the first glance difficult to explain; but it must not be forgotten that we have to do with a softening of only four weeks' duration, which is hardly sufficient to determine a sclerosis appreciable with the Weigert-Pal method. The fact that other tracts, the internal sagittal layer, for instance, already show distinct discoloration, is not contradictory of the above statement. We know that normally, the various tracts differ very considerably in their susceptibilities to staining reagents as regards both rapidity and intensity of reaction; likewise, we know that pathologically, there are appreciable variations in the degree of resistance offered by the individual tracts to degenerative sclerosis.

Here again, outside the vertical segment of the external sagittal layer a well-defined zone of discoloration exists, which can be followed upward

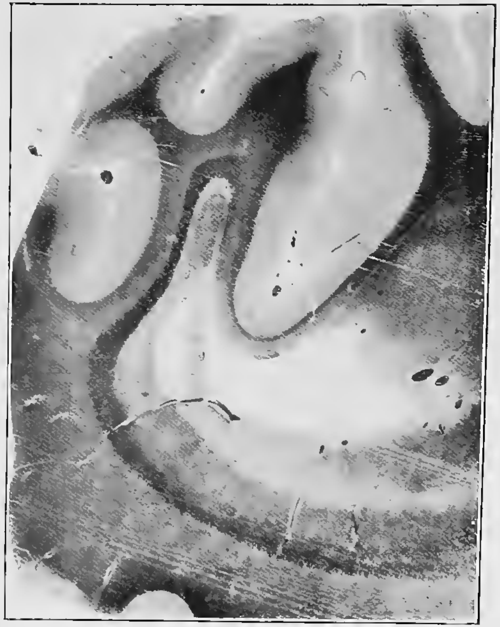
PLATE IV



1



2



3

into the subcortex of the parietal convolutions and mesially beneath the sphenoidal horn into the depth of the gyrus hippocampus; showing that the cingulum derives a fair proportion of its constituent fibres from the convolutions of the temporal convexity. It should be stated that at this level, the domain of the geniculo-calcarine fasciculus is actually occupied in great part by the focus of softening and that the corticifugal projection fibres derived from the mesial convolutions and inferior border of the temporal lobe course through the external sagittal layer; a fact which contributes materially to the relative staining integrity of this layer.

The Marchi sections through the occipital lobe (Pl. IV, Fig. 3) all show abundant granular bodies. In the anterior portion of this lobe, the granular bodies occupy mainly the ventral segment of the external sagittal layer and the corresponding portion of the tapetum; the internal sagittal layer being practically free. As we consider more and more posterior levels, we note that the Marchi granules gradually ascend through the vertical segment of the external sagittal layer until we reach the occipital pole, when it is seen that they have invaded the whole of the external layer, forming practically a closed ring of granular bodies around the internal sagittal layer and the retroventricular callosal stratum. Throughout the posterior portion of the occipital lobe, the granules are essentially confined to the domain of the external layer, which they thickly beset throughout; but they are far more abundant in its ventral than in its dorsal segment. The tapetum and internal sagittal layer contain at this level but few granular bodies. Outside of the external sagittal layer and corresponding to the subcortex of the occipital convexity, a few stray granules are here and there to be seen, which evidently represent degenerated association fibres derived from the temporal lobe. From the superior and inferior horizontally-directed segments of the external sagittal layer, strings of granules are constantly detached which radiate into all parts of the cortex bordering upon the calcarine fissure. In many places the granules may be followed beneath the Gennari line. In their course from the external sagittal layer to the calcarine cortex, the degenerated fibres pass, in considerable numbers, through the internal sagittal layer.

RÉSUMÉ AND INTERPRETATION OF THE VARIOUS DEGENERATIVE SCLEROSES AND NUCLEAR ATROPHIES OBSERVED IN ALL THREE CASES.

In the first place as regards the external sagittal layer, we have seen that its occipital portion degenerates from before backward in cases of deep-seated lesions of the temporal lobe. Twice, once with the Weigert-Pal stain and once with the Marchi method, we have found a complete sclerosis of the external sagittal layer in an otherwise perfectly healthy occipital lobe, induced by extensive foci of encephalomalacia limited to the temporal lobe. We must therefore assume that the course of the constituent fibres of the occipital external sagittal layer is corticipetal. In Case I, in which the softening is confined to the posterior part of the parieto-temporal lobe, we have seen that in the more anterior and normal regions of the temporal lobe, the degenerative sclerosis occupies both the external and internal sagittal layers, but that it is far less voluminous than would be expected from the extensive lesion of the peri-Sylvian convolutions; showing that a fair proportion of the fibres intercepted have become reconstituted in front of the lesion, *i. e.,* that their course must therefore be corticipetal. Under both groups of circumstances then, we have very distinct evidence that the constituent fibres of the occipital external sagittal layer take their origin from some level anterior to that of the pulvinar of the optic thalamus. The actual cases do not permit us to make more definite statements regarding the real source of these fibres, but we have previously demonstrated that anterior temporal lesions limited to the cortex and immediate subcortex determine no appreciable reaction in the domain of the occipital external sagittal layer and that the external geniculate body represents the nucleus of origin of this layer.

We have already sufficiently insisted upon the fact that the external sagittal layer of the temporal lobe is a far more complex structure than that of the occipital lobe and that it is grossly incorrect to regard the one as the unmodified continuation of the other.

The intimacy of relation between projection and association fibres has been a constant feature throughout. Particularly instructive in Case I in which it furnished the motive for comparison of our case with that of von Monakow, this feature was likewise distinctly appreciable in both the other cases. Owing to secondary degeneration, the domain of the external sagittal layer, which, in the normal state, is extremely ill-defined against that of the cingulum in the temporal lobe and that of the bundles of Sachs, Vialet and Wernicke in the occipital lobe, became sharply delimited. The interdependence of the various association tracts is another feature which this series of cases serves to clearly demonstrate. We saw that both divisions of the cingulum, the parietal which courses through the subcortex of the gyrus fornicatus and the temporal which occupies the depth of the gyrus hippocampus, were decidedly affected by lesions of the temporo-parietal convexity; Cases II and III both illustrate this point very distinctly. The cingulum which is generally regarded as being the great association bundle of the mesial hemispheral region is thus likewise related to the lateral convexity, as it receives from the latter territory a considerable number of fibres. We believe that the parietal segment of the cingulum is in relation with the fasciculus arcuatus and the temporal segment with the fasciculus uncinatus. Again, it was observed in Case III, that the lesion in the domain of the fasciculus uncinatus had determined an appreciable discoloration of the fasciculus arcuatus by means of fibres which course upward through the external capsule. It thus becomes apparent that all the association-tracts of the cerebral hemisphere are more or less interdependent.

The tapetum, *i. e.,* the innermost of the deep sagittal layers of the temporo-occipital lobe, that which borders directly upon the ventricular ependyma, is constituted essentially by the fibres of the corpus callosum of which it is simply the intrahemispheral expansion. It abandons fibres to and receives the same from all the convolutions; these fibres traversing in their course the internal and external sagittal layers more or less at right angles. The callosal radiations of the anterior portion of the temporal lobe reach the trunk of the corpus callosum by coursing through the external and internal capsules; a fact well illustrated in Case III. The external capsule is thus in great part tributary of the callosal system, conveying likewise the callosal fibres of the island of Reil.

The tapetum is totally independent from the internal sagittal layer of the fronto-parietal lobe. The statement of Déjerine and others, that lesions of the temporal lobe react upon this layer, is not borne out by the facts observed in our cases. In both Cases II and III, the greater part of the temporal lobe, including the tapetum, is destroyed, and yet we note the persistence of the fronto-parietal internal sagittal layer which is even exceptionally well-defined. This layer, we repeat, is part and parcel of the corona radiata.

In Cases II and III we observed a massive degeneration of the outer division of the pes pedunculi or ventral segment of the cerebral peduncle. This area, as is well known, is the domain of Türck's fasciculus, the constituent fibres of which are derived from the cerebral cortex and pass into the brain-stem through the sublenticular division of the internal capsule. In Case I, in which the lesion is practically confined to the parieto-occipital lobe, involving only the base of the first temporal convolution, there exists no appreciable sclerosis in the domain of the pes pedunculi. The study of these cases shows that the parietal and occipital lobes do not send any fibres into the ventral portion of the brain-stem as was formerly supposed. Türck's fasciculus is derived solely from the cortex of the temporal lobe.

In Cases II and III, in which all connections between the basal ganglia and the calcarine cortex have been destroyed, we note an extreme discoloration and atrophy of the optic pulvinar and anterior corpus quadrigeminum and an atrophy of the external geniculate body. In Case II, owing to retrograde degeneration, this body presents, in addition, a marked discoloration. In all three cases there exists, in keeping with the involvement of the first temporal convolution, a decided atrophy and degeneration of the internal geniculate body; a relation first established by von Monakow and subsequently confirmed by Mahaim, Déjerine and others.

In Cases II and III in which the greater part of the temporal lobe is destroyed, there exists a marked atrophy and degeneration of the mesial nucleus of the optic thalamus; in Cases I and II, in which there is likewise considerable implication of the parietal lobe, we note in addition, a distinct discoloration and atrophy of the dorsal segment of the lateral nucleus.

CONCLUSIONS.

1. The external sagittal layer of the temporo-occipital lobe is composed essentially of projection fibres; its occipital segment is constituted by the geniculo-calcarine fasciculus, the fibres of which take their origin from the external geniculate body and terminate in both the upper and lower lips of the calcarine fissure, but more particularly in the latter.

2. The various association tracts of the cerebral hemisphere are all more or less interdependent and represent topographic subdivisions of one main fibre-system rather than distinct and individual bundles.

3. The tapetum is formed essentially by the fibres of the corpus callosum.

4. The internal sagittal layer of the fronto-parietal lobe is part and parcel of the corresponding portion of the corona radiata and

probably serves to establish the connections between the gyrus fornicatus and the optic thalamus.

5. Türck's bundle takes its origin exclusively from the cortex of the temporal lobe. The parietal and occipital lobes take no part in the constitution of the pes pedunculi or ventral segment of the cerebral peduncle.

6. The existence in the brain of man of an occipito-frontal association bundle is totally inadmissible.

In terminating, I desire to acknowledge my indebtedness to my teacher, Pierre Marie, who has kindly supplied me with the material utilized for this publication.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX, WITH THE REPORT OF TWO CASES.

BY C. W. LOUIS HACKER, M. D.

The present general interest in primary carcinoma of the vermiform appendix, a disease at one time of interest only to the pathologist but now attracting also the attention of the surgeon, appears to warrant the publication of the observations herein detailed. The literature of the subject has been fully covered by recent writers and only a brief summary of it will be given in this report.

Attention was first called to the subject in 1882 by Beger who made a clinical as well as histologic diagnosis. The second case was reported by Stimson in 1896, since when the number has steadily increased. The increase in the number of reported cases is in all probability due to the now almost universal custom of examining microscopically all material removed at operation. I have collected from the literature ninety-five undoubted cases in which a histologic diagnosis was made. These are reported by Burman, Baldauf (3), Barrow, Battle, Becker, Beger, Biggs, Brandt (2), Coons, Cullingworth and Comer, Driessen, Eccles, Elting (2), Giscard, Goffe, Grünbaum, Hammond, Harte (9), Harte and Willson (2), Hurdon, Hessberg, Jessup, Jones and Simmons, Kaufman (2), A. O. J. Kelly (5), Kelly and Hurdon (3), Korte (3), Kudo (4), Landau, LeConte, Lejars, Letulle and Weinberg (8), Lubarsch, Mason and Rhea, McBurney (2), McCosh, McWilliams, Moschcowitz (3), Mosse and Daumic, Myerstein, Neri, Norris, Patel, Regling, Rolleston, Schrumpf, Stimson, Walsham, Warthin, Weber, Weinberg, Weir, Weil, White and Zaaijer (6).

Of the above cases, eight were examined at this laboratory. These, reported by Elting, Baldauf and Harte I shall describe briefly.

I. *Elting*—Mrs. L., thirty-six years of age, had shown no symptoms of appendicitis. A bilateral salpingo-oophorectomy was performed for chronic pelvic inflammation. The appendix, apparently normal, was removed, as a matter of routine, but on microscopic examination was found to be the seat of a small alveolar carcinoma, one cubic centimeter from the proximal end. The lumen was everywhere obliterated.

II. *Elting*—The patient was a male, eighty-one years of age. The appendix was removed at autopsy on an individual whose death was due to pulmonary tuberculosis and cardiac disease. The clinical history presented no symptoms of disease of the appendix. The appendix was free from adhesions and measures five and five-tenths centimeters in length. The distal portion of the organ for a distance of three and five-tenths centimeters was much enlarged (three centimeters in diameter). Projecting from the convex surface of the enlarged portion at about its middle point and opposite the mesenteric attachment was a mass of yellowish green, translucent gelatinous substance. On section through the middle of the organ the lumen was found to be filled with a similar gelatinous material. Sections showed colloid carcinoma.

III. *Baldauf*—Mr. H., thirty-eight years of age, presented symptoms of appendicitis the day before the operation. The appendix was adherent beneath the umbilicus, and was considerably thickened and covered with fibrin. The lumen was patent and the mucosa injected and the seat of small foci of necrosis. The anatomical diagnosis was acute appendicitis and the microscopic diagnosis carcinoma simplex with ulceration, acute appendicitis and periappendicular suppuration.

IV. *Baldauf*—Mr. B., twenty-three years of age, had had three attacks of appendicitis, the last beginning five years before the operation. The appendix was adherent and the lumen obliterated. Microscopic examination revealed an alveolar carcinoma replacing the mucosa and invading the muscularis and, on the mesenteric side, subserous tissue also.

V. *Baldauf*—A girl, eight years of age, presented symptoms of appendicitis, severe in character, two days before the operation. The appendix was surrounded by an inflammatory mass and contained a small amount of pus in its distal portion which was thickened and indurated and surrounded by granulation tissue. The proximal half was normal and the entire lumen patent. The anatomical diagnosis was chronic appendicitis with partial organization of a periappendicular abscess; the microscopic examination revealed an alveolar carcinoma involving the submucosa.

VI. *Harte*—Miss M. A., fourteen years of age, presented a history of acute appendicitis. The appendix was swollen and measured six and five-tenths centimeters in length. The external surface was covered in places by a fibrino-purulent exudate. All coats were thickened and the mucosa presented numerous punctate hemorrhages and small areas of ulceration. At a distance of two cubic centimeters from the proximal end was a slight thickening affecting, particularly, the mucosa. The anatomical diagnosis was acute diffuse and ulcerative appendicitis with fibrino-purulent periappendicitis. The microscopical examination showed an alveolar carcinoma in addition to the acute inflammatory condition.

VII. *Harte*—Miss W. P., thirteen years of age, had a definite history of appendicitis. The appendix was markedly thickened and firmer than normal. To its peritoneal surface were attached numerous firm fibrous tags and one cubic centimeter from the tip was an area of necrosis with perforation. The lumen was patent and the mucosa thickened and studded with minute hemorrhages. An anatomical diagnosis was made of chronic appendicitis with acute exacerbation, gangrene and perforation. The microscopic examination revealed in addition a carcinoma of the appendix.

VIII. *Harte*—Miss K. B., twenty-one years of age, presented a clinical history of appendicitis. The appendix throughout the distal two-thirds was considerably thickened and at the distal extremity had numerous firm tags attached. At the junction of the middle and proximal thirds the lumen was obliterated and the distal end was considerably thickened and filled with a greenish faecal mass. The mucosa of the distal two-thirds showed spots of hemorrhage. Microscopic examination showed in addition to the chronic obliterative appendicitis a primary carcinoma.

In addition to these eight cases observed in this laboratory, I have met with two others during the first year of my service as assistant in surgical pathology. In neither of these was there a history of appendicitis, the appendix in each instance being removed in the course of an operation on other organs. Brief summaries of the clinical histories and pathological examinations follow:

Case I. Records of the Bender Laboratory, Surg. Path. No. 07-557. Clinical History—Mrs. J. M. S., thirty-one years of age, married, entered the Albany Hospital (service of Dr. A. H. Traver) on April 21, 1907. Her family history was uneventful and her past history offered no evidence of disease of the appendix. Since her last menstruation (February 28, 1907) she has had a dull pain in lower abdomen which increased in March and April. Physical examination revealed an old laceration of the perineum and uterine cervix and a purulent discharge from the cervical canal. At the operation on April 22d, the uterine cavity was curetted and the perineum and uterine cervix repaired. On account of a past history of eclampsia a laparotomy was performed to ligate the Fallopian tubes. The right ovary being cystic, a salpingo-oophorectomy was performed. The appendix was removed as a matter of routine. Convalescence was uneventful and the patient has improved in health since the operation.

Pathological Examination.—The specimen consists of an appendix five cubic centimeters in length. The peritoneal surface is normal. The distal half of the organ is thickened and indurated and twice the diameter of the proximal end, the latter being normal. The lumen is patent throughout and the mucosa normal. Anatomical diagnosis was chronic appendicitis.

Microscopic Examination—The mucosa is intact but between the glands of Lieberkühn occasional small areas of newly formed connective tissue are present. Beneath the mucosa are occasional irregular areas of lymphoid tissue. At one side and entirely within the submucosa are areas of densely packed cells, the outlines of which are indistinct but which are of the epithelial type. The nuclei of these cells are round, deeply staining and show no evidence of mitosis. The smaller areas have a tubular arrangement. No direct communication between these areas and the epithelium lining the glands of Lieberkühn or covering the mucosa, is present. Throughout the submucosa and musculature considerable granulation tissue is present. There is a marked infiltration of leucocytes which at one point in the submucosa form a distinct abscess. The peritoneal coat is oedematous and contains a few leucocytes. The blood vessels are engorged. Microscopic diagnosis—carcinoma simplex of the vermiform appendix. Chronic appendicitis.

Case II. Records of the Bender Laboratory, Surg. Path. No. 07-698. Clinical History—Mrs. M. C., thirty-nine years of age, married, multipara, entered the Albany Hospital (service of Dr. J. A. Sampson) on May 7, 1907. The family history is of little importance. Past history reveals no symptoms suggesting appendicitis. *Present illness*—Ten days before admission to the hospital patient had an acute attack of pain in the lower abdomen associated with fever. No diagnosis was made and the findings at the operation, ten days later, failed to disclose any cause for the symptoms. The diagnosis was made on admission of weakened pelvic floor with retroflexed uterus. At the operation on May 10th a retroflexed uterus was fixed. As a matter of routine the appendix was examined and as a small nodule was felt the appendix was removed. The pelvic floor was then repaired. The convalescence was uneventful. The patient has been in excellent health since the operation.

Pathological Examination. Specimen consists of an appendix measuring six centimeters in length and having a mesentery attached. About five millimeters from the tip it is bent upon itself beyond which is a constriction due to a fibrous band passing around it. Between the distal end and the mesentery a distinct band of adhesions is present. At the junction of the middle and distal thirds is another constriction. The blood vessels of the peritoneum are engorged. On section the lumen of the distal third is found to be obliterated by scar tissue. The remaining mucosa is normal in color but slightly thickened. Anatomical diagnosis—chronic appendicitis with partial obliteration.

Microscopic Examination. Sections are from that portion of the appendix which is bent upon itself. No lumen is present and the mucosa and submucosa are apparently replaced by very cellular young connective tissue which at one place extends down to the musculature. The remaining submucosa is composed of a fat and dense connective tissue. Close to what appears to have been the lumen are numerous areas of densely packed polyhedral cells, the nuclei of which are large, round and contain a fair amount of chromatin. No mitotic figures are present. The protoplasm is small in amount and no intercellular substance is visible. About these areas a small amount of connective tissue is present. The internal muscular layer contains numerous small, round and epithelioid cells. The blood vessels of the peritoneum are dilated. Microscopic diagnosis—carcinoma simplex of the vermiform appendix; chronic obliterative appendicitis.

These two cases with the three reported by Harte give a total of five primary cancers of the appendix observed in this laboratory during the past four years (Sept. 1, 1904 to Sept. 1, 1908) in a series of 1298 appendices removed at operation and examined microscopically. The proportion of cancer is therefore as 1 to 260 or approximately four-tenths of one per cent. If to these five are added the five reported by Elting and Baldauf, we have ten carcinomata observed in one laboratory in a period of twelve years in the routine examination of 2033 appendices, a proportion of 1 to 203, or practically one-half of one per cent.

From a review of these cases little that is new can be presented. The symptomatology if symptoms be present, is that of either acute or chronic appendicitis. The vermiform appendix having no striking function to perform, the presence of a neoplasm in the absence of inflammation would not produce symptoms pathognomonic of a physiological disturbance. The only symptom in the early stage might be pain due to pressure upon the sensory nerves or to obstruction of the lumen. The vast majority of cases in which pain was present gave, however, a history of recurrent attacks more characteristic of chronic inflammation than of carcinoma. It is noteworthy that of the thirty-two out of ninety-six cancerous appendices presenting no symptoms and removed at autopsy or during operation for other lesions, only four appeared normal to the naked eye. All others showed macroscopic changes, usually inflammatory in nature, suggesting the advisability of removal. Three of these apparently normal showed on section a chronic obliterative appendicitis in addition to carcinoma. Another argument is therefore offered for the removal, in the course of abdominal operations of every appendix showing evidence of disease.

Age plays a very important role for in youth carcinoma occurs with greater frequency in the appendix than in any other organ of the body. Of ninety-one cases in which the age is given, the average was twenty-nine and one-tenth years. In females it was twenty-eight and one-tenth and in males thirty and three-tenths years. The youngest was eight and the oldest, eighty-one. One may judge from the following table the frequency with which this disease occurs during the various decades of life.

3.29	per cent.	during	the	1st	decade
16.48	"	"	"	2nd	"
39.56	"	"	"	3rd	"
27.47	"	"	"	4th	"
5.49	"	"	"	5th	"
4.39	"	"	"	6th	"
0.00	"	"	"	7th	"
2.19	"	"	"	8th	"
1.09	"	"	"	9th	"

Cancer of the appendix occurs more frequently in the female than in the male. Of eighty-eight cases, fifty-four or sixty-one and three-tenths per cent. were in females whereas only thirty-four or thirty-eight and seven-tenths per cent. were in males. A possible explanation may be the greater frequency of laparotomy on the female. About one-fifth of the cancers in women were found accidentally during laparotomy for other conditions.

Numerous observations both clinical and anatomical suggest very strongly that carcinoma of the appendix is secondary to chronic inflammation. While the appendix is an organ which undergoes atrophy this apparently does not predispose it to carcinomatous change. The period of life during which these cases most frequently occur, corresponds to that of chronic appendicitis and not atrophy. Clinically, forty-seven per cent. of the cases presented symptoms of chronic appendicitis but histologically nearly all appendices were the seat of chronic inflammation. In twenty-eight per cent. also an obliterative appendicitis was present.

In this connection Ribbert's theory would appear to offer an explanation of the development of carcinoma in the appendix. In chronic appendicitis the connective tissue changes are most marked about the glands of Lieberkühn so that a portion of the cells might become detached by cicatricial contraction and continue to proliferate; or during obliteration a portion of the mucosa may become included within the scar.

The anatomical diagnosis is usually difficult if adjacent structures are involved or metastatic nodules are present in other viscera. The appendix in twenty-three of eighty-five cases presented a tumor as it lay in the abdomen; in twenty-four the tumor was discovered after removal; in the remainder the tumor was discovered only upon microscopic examination. This emphasizes the importance of examining microscopically every diseased appendix.

The most frequent site at which carcinoma is found is the tip. Of seventy-eight cases in which the location is mentioned it involved in forty-eight the distal extremity.

Carcinoma of the appendix may be of any of the types found elsewhere in the intestines but the spheroidal cell cancer is the most frequent. Of those reported in detail sixty-one and five-tenths per cent. were spheroidal cell, thirty-six per cent. glandular, and two and five-tenths per cent. colloid.

The tumor is usually limited to the mucosa and submucosa. In only thirty of the seventy-eight analyzed did it extend to the subserosa or serosa. Infiltration is apparently along the lymphatics to the mesentery for in six cases it was most pronounced opposite the menenteric attachment and in nine the mesentery was involved.

Metastases are not often found but this may be due to the early removal of the primary growth. Metastatic growths were present in the retroperitoneal lymph nodes in two cases and in the ileo-colic in one. One case died with general metastasis and in one were multiple nodules beneath the peritoneum. The cecum was involved in only two cases.

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BENDER HYGIENIC LABORATORY.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1908.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1908.

The Work of the Laboratory.—The routine examinations of all kinds are summarized in the following table: no important changes in the character of this work have occurred.

TABLE I. ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1907 TO AUGUST 31, 1908.

	Albany Hospital.	St. Peters Hospital.	Childs' Hospital and St. Margarets House.	State Department of Health.	City Department of Health.	All other sources.	Totals.
Autopsies	42	6	2	......	......	84	134
Surgical Specimens	1,043	507	19	......	......	140	1,709
Gen. Bacteriology and Clin. Microscopy	388	92	6	3,273	2,348	227	6,334
Totals	1,473	605	27	3,273	2,348	451	8,177

Laboratory courses for undergraduates of the Albany Medical College have been given as follows:

1. Normal Histology.—Drs. Beilby and Douglas, six hours a week.

2. Pathology and Bacteriology.—Drs. Pearce, Sawyer, Hawn and Doescher, eight hours a week.

3. Clinical Microscopy.—Drs. Hawn, Sawyer and Rulison, two and a half hours a week (Dr. Laird on leave of absence).

4. Surgical Pathology.—Drs. Elting, Hacker and Sibley, two and a half hours a week.

5. Histology and Pathology, in connection with the course in Obstetrics.—Drs. Lipes and Douglas, two and a half hours a week.

6. Anatomy and Pathology of the Nervous System.—Dr. Archambault, two and a half hours a week.

7. Experimental Physiology (Second year).—Dr. Jackson, five hours a week during first half year.

8. Experimental Physiology (First year).—Dr. Becker, two hours a week.

Among those who have availed themselves of the opportunity to work in the Laboratory for considerable periods of time are, Drs. J. A. Sampson of Albany, E. J. Buchan of Chicago, B. F. May of New York City, J. Wingate of Schenectady, W. C. Treder of Syracuse, H. H. Drake of Albany, and Messrs. Nelson Fromm, E. S. Haswell and W. A. Bing of the Albany Medical College, and L. W. Gorham and A. W. Morrison of the Johns Hopkins Medical School and Mr. George W. V. Spellacy of the New York State Department of Agriculture. These have assisted in the routine work of the Laboratory, pursued special lines of study or engaged in research work.

Investigations undertaken during the year are as follows:

1. Hacker, C. W. L., The Appearance of Glycuronic Acid in Certain Conditions of Diminished Oxidation, *Jour. Am. Med. Assoc.*, 1908, L, 252.

2. Beilby, G. E., A Clinical Study of Hypernephroma with Pathological Reports, *Surgery, Gynecology and Obstetrics*, 1908, Sept., 279.

3. Pearce, R. M., The Influence of the Reduction of Kidney Substance upon Nitrogenous Metabolism, *Journal of Experimental Medicine*, 1908, X, 632.

4. Pearce, R. M. and Sawyer, H. P., Concerning the Presence of Nephrotoxic Substances in the Serum of Animals with Experimental Nephritis, *Journal of Medical Research*, 1908, XIX, 269.

5. Sampson, J. A. and Pearce, R. M., A Study of Experimental Reduction of Kidney Tissue with Special Reference to the Changes in that Remaining, *Journal of Experimental Medicine*, 1908, X, 745.

6. Pearce, R. M., The Relation of the Adrenal Gland to Chronic Nephritis and to Arteriosclerosis: An Anatomical Study, *Journal of Experimental Medicine*, 1908, X, 735.

7. Jackson, H. C. and Elting, A. W., Clinical Notes and Physico-Chemical Study of Salt Elimination in the Urine of an Individual with General Oedema of Obscure Origin, Followed by Cure, *The Archives of Internal Medicine*, 1908, II.

8. Pearce, R. M., A Note on the Occurrence of Spontaneous

Arterial Degeneration in the Rabbit, *Jour. of Am. Med. Assoc.*, 1908, LI, 1056.

9. Jackson, H. C., The Effect of Conditions upon the Latent Period and Rate of Aseptic Post Mortem Autolysis during the First Ten Hours, *Journal of Experimental Medicine*, 1909, XI, 55.

10. Archambault, L., The Inferior Longitudinal Bundle and Geniculo-Calcarine Fasciculus.

11. Hacker, C. W. L., Primary Carcinoma of the Vermiform Appendix with Report of Two Cases.

12. Jackson, H. C., Hawn, C. B. and Sawyer, H. P., A Study of Normal Daily Variations in the Physical and Chemical Composition of the Blood in Relation to Normal Opsonic and Phagocytic Indices (in press).

13. Jackson, H. C., Hawn, C. B. and Sawyer, H. P., The Influence of Variations in Osmotic Pressure of Blood and Serum upon Opsonic and Phagocytic Indices (in press).

14. Jackson, H. C. and Baldauf, L. K., A Chemical Study of the Liver during Fatty Transformation (in press).

15. Jackson, H. C. and Hawn, C. B., Note on the Sterility of Living Organs (Dog) (uncompleted).

16. McDonald, E., Sarcoma of the Uterus, with Report of Nine Cases.

17. Elting, A. W. and Tredway, E. E., Hereditary Gangrene in Early Life due to Endarteritis.

18. McDonald, Ellice and Krieger, W. A., Bilateral Tubal Pregnancy, with Report of Two Cases.

19. Hacker, C. W. L., Carcinoma of the Umbilicus.

20. Archambault, L., Contribution to the Anatomy and Pathogeny of Angenesia of the Corpus Callosum.

Of these investigations, the third to sixth inclusive and the eighth, ninth, twelfth, and fourteenth were conducted under grants made to the Director and Dr. H. C. Jackson by the Rockefeller Institute for Medical Research; the first, seventh and thirteenth under similar grants from the Committee on Scientific Research of the American Medical Association.

Changes in the Staff.—The changes in the staff this year are quite general. My own resignation takes effect September first, in order that I may accept the Professorship of Pathology at the New York University and Bellevue Hospital Medical College of New York City. Drs. H. P. Sawyer and C. B. Hawn terminate their connection with the Laboratory on August 31st; the former accompanies me to New York to become Instructor in Pathology in the New York University and Bellevue Hospital Medical College; the latter enters general practice in Albany. To one of these vacancies has been appointed M. D. Cronin (M. D., Albany Medical College, 1907); the other has not yet been filled. Dr. C. W. L. Hacker resigned June 1st to enter private practice and has been succeeded by J. L. Bendell (A. B., Yale, 1903, M. D., Albany Medical College, 1907). Dr. T. F. Doescher resigned July 1st to become an assistant to Dr. Albert Vander Veer and in his place has been appointed L. H. Gaus (M. D., Albany Medical College, 1907). R. C. Keigher (M. D., Albany Medical College, 1907) has been appointed Pathological House-Officer by the Board of Governors of Albany Hospital to succeed Dr. W. A. Krieger, who resigned July 1st to accept the position of Pathologist to the Vassar Hospital of Poughkeepsie, N. Y.

Work of the Past Five Years.—As this report marks the completion of my five years' service as Director, I append a table showing the activities of the laboratory during this period. This table with that which appeared in my Third Annual Report (1906) represent graphically the work and development of the laboratory since its opening in 1896.

TABLE II. SUMMARY OF WORK OF PAST FIVE YEARS, 1903-1908.[1]

	1904	1905	1906	1907	1908	Totals	Average
Autopsies	123	129	120	135	134	641	128
Surgical Specimens	1,003	1,271	1,471	1,617	1,709	7,071	1,178
Gen. Bacteriology and Clin. Microscopy	2,515	2,683	2,961	5,725	6,334	20,218	4,043
Totals	3,641	4,083	4,552	7,477	8,177	27,930	....
Laboratory Courses	6	6	6	8	8	......	....
Publications	11	8	17	12	11	......	....

Worthy of special mention is the development of the Department of Physiological Chemistry under the able direction of Dr. H. C. Jackson. This department, established three years ago, has been of great value in connection with the routine work and has added vastly, as may be seen in the titles of published investigations, to the possibilities of co-operation in research work. Dr. Jackson's relation to the laboratory work, both routine and experimental, has been very intimate and has made it possible to apply to any problem the methods of physiology and chemistry in addition to those of pathology and bacteriology.

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[1] Each yearly period ending August 31st.

I therefore take this opportunity to express my appreciation of the great value to the laboratory of Dr. Jackson's work and also of his very cordial co-operation during the past three years. Moreover I would suggest to your board the appointment of an additional assistant to aid in the further development of this very important aspect of laboratory effort.

The Bender Laboratory Club.—This organization continues to be a most important feature of the laboratory life. The guests during the past year were Dr. Warfield T. Longcope, Director of the Ayer Laboratory of the Pennsylvania Hospital of Philadelphia who discussed our newer knowledge of Hodgkin's disease and Dr. Henry A. Christian, Assistant Professor of Medicine at the Harvard Medical School, who presented a general review of recent work on "Experimental Nephritis."

"Studies from the Bender Laboratory."—The fifth volume of this laboratory publication will appear at the end of the present year. In the first volume (1904) was incorporated a short sketch of the history of the laboratory together with a list of previous publications under Dr. Blumer's directorship and portraits of the founder and the first director. In this, as in succeeding volumes, all papers published from the laboratory have been reprinted in full and in each also the annual report of the director, summarizing all activities of the laboratory, changes in staff and other items of interest, has appeared. These volumes thus present, in complete form, the work and publications of the laboratory and constitute as well a general history of the institution. They have been so favorably received that it is to be hoped that your board will see its way clear to continue this annual publication.

Gifts.—It is a great pleasure to acknowledge the financial support which has been rendered by Drs. Albert Vander Veer, Henry Hun, W. G. Macdonald, Arthur W. Elting, A. H. Traver and C. F. Theisen. These gentlemen have contributed funds which have been used for special assistants in surgical pathology and neuro-pathology, for apparatus, and to a small extent for defraying the expenses of the last volume of "Studies from the Bender Laboratory." To Dr. Henry Hun we are also indebted for a set of lower power lenses for use with the microscope attachment of the projection lantern. This very general assistance, which may be taken as an appreciation of the usefulness of the laboratory, argues well for its support and development in the future.

Finally, as this report marks the end of my directorship, I wish to express my appreciation of the interest which your board has always shown in the work of the laboratory as well as of your ready co-operation in the development of its activities. The five years during which I have been associated with the Bender Laboratory have been most helpful to me and represent a period of my experience as pathologist to which I will always look back with the greatest pleasure and satisfaction. If, on the other hand, I have helped you, as I sincerely hope I have, to develop the influence of the Bender Laboratory and to advance the spirit of scientific medicine in Albany, there will be the added satisfaction that others than myself have profited by our mutual efforts.

Respectfully submitted,
RICHARD M. PEARCE,
August 31, 1908. *Director.*

Robert G. Scherer

In Memoriam

Robert G. Scherer was born in Albany, N. Y., March 20, 1861, his father being a prominent merchant of that day. His education was obtained in the public and private schools of this city and in his father's store and at the Commercial College he received a thorough business training. Adopting law as his profession, young Scherer at an early age entered, as clerk, the law office of Paddock, Draper and Chester. After several years spent in this office he attended Cornell University and was graduated from Columbia Law School. About 1881 he formed a law partnership with John F. Montignani which continued for some years. On the dissolution of this firm he was associated with J. Murray Downs and Neile F. Towner. In 1884 he married Anna, daughter of James T. Story of Albany, N. Y., and she with one daughter survive him. In 1898 he was appointed Miscellaneous Court Reporter and so well was his work in this position approved by his profession that his reappointment in 1903 was received with entire satisfaction.

As a lawyer Robert G. Scherer was highly esteemed. He appeared frequently at Special Term and in the Appellate Division and Court of Appeals. He was widely known as a counsellor and adviser in matters of public and private business. Few men of his years in so arduous and exacting a profession accomplished more or attained such eminence.

Mr. Scherer was a Republican; a member of the Board of Public Instruction of the City of Albany from 1885 to 1889 and introduced many reforms in the school system; a member of Assembly from Albany County in 1896 and 1897 and Chairman of the Judiciary Committee; and a member of the Committee on Law Reform of the State Bar Association. He was a prominent Mason.

The characteristics that won for Robert G. Scherer social, political and professional prominence were his thoughtfulness, thoroughness and efficiency. He was of a quiet and almost retiring disposition but possessed a charm of manner and cheerfulness of temperament with a natural kindliness of heart that made him always friendly, affable and genial.

Mr. Scherer's admirable qualities were best illustrated by the fact that although his life was filled to overflowing with varied work and manifold interests connected intimately with his professional and public activities he gave freely of his time and intelligence to the management of the Albany Hospital with which institution he was for many years connected and of which he was a Governor at the time of his decease.

In the encouragement of medical science as in all matters philanthropic, Mr. Scherer manifested the greatest interest. This drew him into heartiest collaboration with Mr. Matthew Bender, the founder of the Bender Hygienic Laboratory for which institution he prepared the constitution and by-laws. He served as President of the Trustees of the Laboratory from February 23, 1904 until his death.

After a lingering illness Mr. Scherer died at his home on Madison Avenue in this city on October 28, 1905 at the early age of forty-four years.

As a tribute of their respect for their late President the Trustees of the Bender Hygienic Laboratory passed the following resolution and placed it upon the minutes.

By the sad and untimely death of Robert G. Scherer, which occurred at his home November 1, 1905, the Board of Trustees of The Bender Hygienic Laboratory lost one of its most valued and faithful members.

Mr. Scherer has been identified with the Bender Laboratory since its inception. As a friend and the attorney of Mr. Matthew Bender, the donor of the Laboratory Building, Mr. Scherer advised with and aided in directing and carrying out Mr. Bender's wishes in the erection of the Laboratory. In securing from the City of Albany the site and in the organization of the corporation, Mr. Scherer took the most active part. He met with us at the organization of the Board June 27, 1905, and has been in continuous service on the Board since—acting as its legal adviser and performing all other duties pertaining to his trusteeship with the deepest interest and fidelity, and we record to-day the expression of the high esteem and regard in which he was held, and our appreciation of his valued services on the Board.

We direct, by resolution, that a copy of this record be mailed to his bereaved family, together with the expression of our deepest sympathy to them in this hour of their great sorrow.